IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Bernd RIEDL et al.		Confirmation No.:	3172
Serial No.:	10/086,417	Examiner:	Henley III, Raymond J
Filed:	March 4, 2002	Group Art Unit:	1614

Title: OMEGA-CARBOXY ARYL SUBSTITUTED DIPHENYL UREAS AS p38 KINASE INHIBITORS

SUPPLEMENTAL REPLY AND INFORMATION DISCLOSURE STATEMENT

MAIL STOP NON FINAL
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Response filed on December 8, 2006 (copy attached), Applicants submit this Supplemental Reply and Information Disclosure Statement.

A copy of the claims in the following co-pending application is attached.

09/889,227
10/071,248
09/948,915
10/361,858
09/993,647
10/042,203
10/361,859
10/308,187
10/895,985

Applicants have resubmitted the references AA-BM on pages 6-8 of the PTO-1449 form filed October 4, 2005. The Examiner indicated copies of these references could not be located on the disc provided and struck through them on the PTO-1449 Form.

Respectfully submitted,

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Attorney Docket No.: **BAYER-0016-P04**

Date: **December 15, 2006**

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. **(Currently Amended)** A compound of Formula I:

$$A - D - B \qquad (I)$$

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of the formula:

$$-L-M-L^1,$$

wherein L is phenyl, optionally substituted by halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl up to perhaloalkyl and C_1-C_3 alkoxy L^1 is selected from pyridinyl substituted by $-C(O)R_x$, and

optionally substituted with 1-3 additional substituents independently selected from the group consisting of R^7 and halogen;

wherein R_x is NR_aR_b and R_a and R_b are

A) independently

a) hydrogen,

b) C_1-C_{10} alkyl,

c) C_6 aryl,

d) pyridinyl

e) substituted C_{1-10} alkyl,

f) substituted C_6 aryl,

g) substituted pyridinyl

h) -phenylpiperazine(pyridinyl),

i) -phenylmorpholinyl,

j) -ethylmorpholinyl,

k) -ethylpiperidyl,

l) -methyl pyrrolidinyl,

m) -methyl tetrahydrofuryl,

or

n) $-C_2H_4NH$(phenyl);

where when R_a and R_b are a substituted group, they are substituted by

a) halogen up to per halo,

b) hydroxy,

c) $-N(CH_3)_2$,

d) C_1-C_{10} alkyl,

e) C_1-C_{10} alkoxy,

f) halosubstituted C_{1-6} alkyl, or

g) $-OSi(Pr\text{-}i)_3$; or

B) R_a and R_b together form piperazine or a substituted piperazine with substituents selected from the group consisting of

a) halogen,

b) hydroxy,

c) C_{1-10} alkyl,

d) pyridinyl

e) C_{1-10} alkoxy,

f) C_6 aryl,

~~h)~~ g) halo substituted C_6 aryl, and

~~i)~~ h) N-(4-acetylphenyl);

M is selected from the group consisting of oxygen and sulfur;

and

B is

phenyl, substituted with 1-3 substituents independently selected from the group consisting of halogen and R^7,

and R^7 is

(a) C_1-C_6 linear or branched alkyl, optionally substituted with 1-3 halogen substituents; or

(b) C_1-C_6 linear or branched alkoxy.

2. (Canceled)

3. (Previously Presented) A compound as in claim 1 wherein M is oxygen .

4. (Previously Presented) A compound as in claim 1 wherein the cyclic structures of B and L bound directly to D are substituted in the ortho position by hydrogen.

5. (Canceled)

6. (Currently Amended) A compound of claim 1 wherein B of Formula I is phenyl, substituted with 1-3 substituents independently selected from the group consisting of ~~halogen~~ chlorine, C_1-C_6 alkoxy or up to per halo substituted C_1-C_6 alkyl.

7. (Currently Amended) A compound of claim 3 wherein B of Formula I is

phenyl, substituted with 1-3 substituents independently selected from the group consisting of ~~halogen~~ chlorine, C_1-C_6 alkoxy, or substituted C_1-C_6 alkyl, substituted by one or more halogen substituents.

8. (Currently Amended) A compound of claim 4 wherein B of Formula I is phenyl, substituted 1 to 3 times by 1 or more substituents selected from the group consisting of ~~halogen~~ chlorine, C_1-C_6 alkoxy or up to per halo substituted C_1-C_6 alkyl.

9. (Previously Presented) A compound of claim 1, wherein L is phenyl, optionally substituted by halogen up to perhalo.

10. (Previously Presented) A compound of claim 1, wherein L is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of halogen and C_1-C_3 alkoxy.

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Previously Presented) A compound of claim 4, wherein M is -O- .

19. (Previously Presented) A compound of claim 8 wherein M is -O-.

20. (Previously Presented) A compound of claim 9 wherein M is -O-.

21. (Previously Presented) A compound of claim 10 wherein M is -O- .

22. (Previously Presented) A compound of claim 1 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_6 alkyl, halogen and C_1-C_6 alkoxy.

23. (Previously Presented) A compound of claim 3 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_6 alkyl, halogen and C_1-C_6 alkoxy.

24. (Previously Presented) A compound of claim 18 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_6 alkyl, halogen and C_1-C_6 alkoxy.

25. (Previously Presented) A compound of claim 19 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_6 alkyl, halogen and C_1-C_6 alkoxy.

26. (Previously Presented) A compound of claim 20 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_6 alkyl, halogen and C_1-C_6 alkoxy.

27. (Previously Presented) A compound of claim 21 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_6 alkyl, halogen and C_1-C_6 alkoxy.

28. (Canceled)

29. (Canceled)

30. (Canceled)

31. (Canceled)

32. (Canceled)

33. (Previously Presented) A compound of claim 3 wherein R_a and R_b are independently hydrogen or C_1-C_6 alkyl.

34. (Previously Presented) A compound of claim 18 wherein R_a and R_b are independently hydrogen or C_1-C_6 alkyl.

35. (Previously Presented) A compound of claim 19 wherein R_a and R_b are independently hydrogen or C_1-C_6 alkyl.

36. (Previously Presented) A compound of claim 20 wherein R_a and R_b are independently hydrogen or C_1-C_6 alkyl.

37. (Previously Presented) A compound of claim 21 wherein R_a and R_b are independently hydrogen or C_1-C_6 alkyl.

38. (Previously Presented) A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is of the formula: -L-M-L^1, wherein

L is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl up to perhalo, C_1-C_3 alkoxy and halogen;

L^1 is pyridinyl, substituted by -$C(O)R_x$;

wherein R_x is NR_aR_b and R_a and R_b are independently

hydrogen,

C_1-C_{10} alkyl,

C_6 aryl,

pyridinyl, substituted C_{1-10} alkyl,

substituted C_6 aryl, or

substituted pyridinyl,

where R_a and R_b are a substituted group, they are substituted by halogen up to per halo; and

M is selected from the group consisting of oxygen and sulfur

and

B is phenyl, substituted with 1-3 substituents independently selected from the group consisting of R^7 and halogen;

and R^7 is

(a) C_1-C_6 linear or branched alkyl, optionally substituted with 1-3 halogen substituents; or

(b) C_1-C_6 linear or branched alkoxy.

39. (Previously Presented) A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is of the formula: -L-M-L^1,

L is phenyl,

M is -O-,

L^1 is pyridinyl substituted by $-C(O)R_x$,

wherein R_x is NR_aR_b and R_a and R_b are independently

hydrogen,

C_1-C_{10} alkyl,

C_6 aryl,

pyridinyl,

substituted C_{1-10} alkyl,

substituted C_6 aryl, or

substituted pyridinyl

where R_a and R_b are a substituted group, they are substituted by halogen up to per halo,

and

B is a phenyl group substituted by trifluoromethyl or tert-butyl, and optionally additional substituents selected from the group consisting of halogen up to per halo, and W_n where n is 0-3, and each W is independently selected from the group consisting of

C_1-C_{10} alkyl,

C_1-C_{10} alkoxy,

C_6 aryl,

pyridinyl,

and substituted C_1-C_{10} alkyl, substituted by one or more substituents independently selected from the group consisting of halogen up to per halo.

40. (Previously Presented) A compound as in claim 38 wherein the cyclic structures of B and L bound directly to D are substituted in the ortho position by hydrogen.

41. (Canceled)

42. (Previously Presented) A compound as in claim 39 wherein the cyclic structures of B and L bound directly to D are substituted in the ortho position by hydrogen.

43. (Canceled)

44. (Previously Presented) A compound as in claim 38 wherein substituents for B, are selected from the group consisting of up to per halo substituted C_1-C_6 alkyl and halogen.

45. (Previously Presented) A compound as in claim 39 wherein the optional substituents for B are selected from the group consisting of up to per halo substituted C_1-C_6 alkyl and halogen.

46. (Canceled)

47. (Canceled)

48. (Canceled)

49. (Canceled)

50. (Previously Presented) A pharmaceutically acceptable salt of a compound of formula I of claim 1 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

51. (Cancelled)

52. (Canceled)

53. (Previously Presented) A pharmaceutically acceptable salt of a compound of claim 38 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

54. (Previously Presented) A pharmaceutically acceptable salt of a compound of claim 39 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

55. (Previously Presented) A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt of a compound of formula I, and a physiologically acceptable carrier.

56. (Canceled)

57. (Canceled)

58. (Previously Presented) A pharmaceutical composition comprising a compound of formula I of claim 38 or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

59. (Previously Presented) A pharmaceutical composition comprising a compound of formula I of claim 39 or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

60. (Canceled)

61. (Cancelled)

62. (Currently Amended) A method for inhibiting the enzyme raf kinase in a human or animal, comprising administering a pharmaceutically acceptable amount of a compound of Formula I of claim 1 to said mammal.

63. (Canceled)

64. (Currently Amended) A method for inhibiting the enzyme raf kinase in a human or animal, comprising administering a pharmaceutically acceptable amount of a compound of Formula I of claim 38 to said mammal.

65. (Currently Amended) A method for inhibiting the enzyme raf kinase in a human or animal, comprising administering a pharmaceutically acceptable amount of a compound of Formula I of claim 39 to said mammal.

66. (Canceled)

67. (Canceled)

68. (Previously Presented) A compound of claim 1 wherein the optional substituents on L^1 are selected from the group consisting of methyl, triflouromethyl, methoxy, Cl and F.

69. (Previously Presented) A compound of claim 1 wherein the substituents of B and L are independently selected from the group consisting of methyl, triflouromethyl, tert-butyl, methoxy, Cl, and F.

70. **(Currently Amended)** A pharmaceutical composition ~~for the treatment of a cancerous cell growth~~ comprising a compound of formula I of claim 1 or a pharmaceutically acceptable salt of a compound of formula I and a physiologically acceptable carrier.

71. **(Previously Presented)** A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of the formula: -L-M-L^1,

wherein L is phenyl, optionally substituted with substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, C_1-C_5 alkyl substituted by halogen and C_1-C_5 alkoxy;

L^1 is pyridinyl, substituted with -C(O)NR^aR^b and optionally substituted with one or two substituents selected from the group consisting of R^7, OR^7 and halogen, wherein R^7 is hydrogen, C_1-C_5 alkyl or C_1-C_5 alkyl substituted by halogen,

wherein R^a and R^b independently are

a) hydrogen or

b) C_1-C_5 alkyl;

B is phenyl, substituted by tert-butyl or trifluoromethyl and optionally substituted with additional substituents independently selected from the group consisting of

a) halogen,

b) C_1-C_5 alkyl substituted by halogen or

c) C_1-C_4 alkoxy.

72. **(Currently Amended)** A pharmaceutical composition ~~for the treatment of a cancerous cell growth~~ as in claim ~~71~~ 70 wherein the pharmaceutically acceptable salt is

a) a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

73. **(Canceled)**
74. **(Canceled)**
75. **(Canceled)**
76. **(Canceled)**
77. **(Canceled)**
78. **(Canceled)**
79. **(Canceled)**
80. **(Canceled)**
81. **(Canceled)**
82. **(Canceled)**
83. **(Canceled)**
84. **(Canceled)**
85. **(Canceled)**

86. (Canceled)

87. (Canceled)

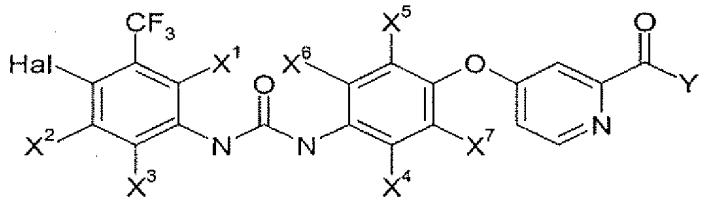
88. (Canceled)

89. (Cancelled)

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Original) A compound of formula (Ia)



(Ia)

wherein,

Y is NHR,

Hal is chlorine or bromine,

R is H, CH_3 or CH_2OH, and

X^1 to X^7 are each, independently, H, OH or -OC(O)C_1-C_4 alkyl,

or a salt or purified stereoisomer thereof,

with the proviso that at least one of X^1 to X^7 is OH or -OC(O)C_1-C_4 alkyl.

2. (Original) A compound of claim 1 wherein X^1 is OH or -OC(O)C_1-C_4 alkyl.

3. (Original) A compound of claim 1 wherein X^2 is OH or -OC(O)C_1-C_4 alkyl.

4. (Original) A compound of claim 1 wherein X^3 is OH or -OC(O)C_1-C_4 alkyl.

5. (Original) A compound of claim 1 wherein X^4 is OH or -OC(O)C_1-C_4 alkyl.

6. (Original) A compound of claim 1 wherein X^5 is OH or -OC(O)C_1-C_4 alkyl.

7. (Original) A compound of claim 1 wherein X^6 is OH or -OC(O)C_1-C_4 alkyl.

8. (Original) A compound of claim 1 wherein X^7 is OH or -OC(O)C_1-C_4 alkyl.

9. (Original) A compound of claim 1 wherein Hal is chlorine.

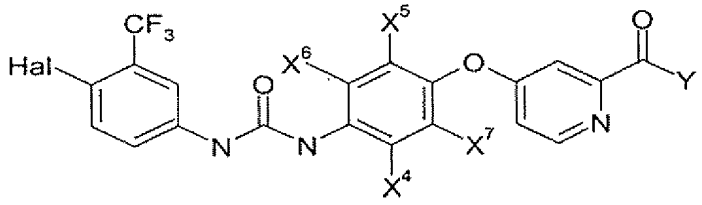
10. (Original) A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]2-(hydroxy)phenoxy}-2-pyridine carboxamide.

11. (Original) A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]3-(hydroxy)phenoxy}-2-pyridine carboxamide.

12. (Original) A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]5-(hydroxy)phenoxy}-2-pyridine carboxamide.

13. (Original) A compound of claim 1 which is 4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]6-(hydroxy)phenoxy}-2-pyridine carboxamide.

14. (Original) A compound of formula (Ib)



(Ib)

wherein,

Y is NHR,

Hal is chlorine or bromine,

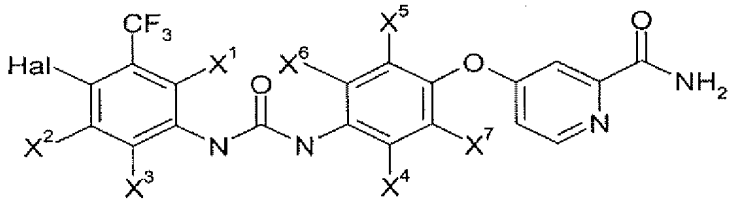
R is H, CH_3 or CH_2OH, and

X^4 to X^7 are each, independently, H, OH or -OC(O)C_1-C_4 alkyl,

or a salt or purified stereoisomer thereof,

with the proviso that at least one of X^4 to X^7 is OH or -OC(O)C_1-C_4 alkyl.

15. (Currently Amended) A compound of formula (Ic)



(Ic)

wherein,

Hal is chlorine or bromine, and

X^1 to X^7 are each, independently, H, OH or -OC(O)C_1-C_4 alkyl,

or a salt or purified stereoisomer thereof,

with the proviso that at least one of X^1 to X^7 is OH or -OC(O)C_1-C_4 alkyl.

16. (Cancelled)

17. (Cancelled)

18. (Cancelled)

19. (Cancelled)

20. (Cancelled)

21. (Cancelled)

22. (Previously Presented) A method of treating osteoporosis and inflammation, in a mammal by administering an effective amount of a compound of claim 1 to said mammal.

23. (Cancelled)

23. (Cancelled)

24. (Cancelled)

25. (Cancelled)

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. **(Currently Amended)** A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L^1)$_q$, where L is a 6 membered cyclic structure, which is substituted phenyl or unsubstituted phenyl, bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members which is phenyl or pyridinyl,

M is a bridging group which comprises ~~comprise~~ -O-, -S-, or -NR^7- ~~—N(R^7)-,~~ wherein R^7 is hydrogen, q is an integer of from 1-3; and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D which is phenyl or pyridinyl,

wherein L^1 is substituted by -C(O)R_x,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C_{7-24} alkaryl, C_{7-24} or aralkyl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from O, N

and S, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from O, N and S, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, or C_7-C_{24} alkaryl, and is optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g and are optionally substituted by halogen, or

-OSi(R_f)$_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_{1-10} alkyl, C_{1-10} alkoxy, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{6-12} aryl, C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, S and N, or C_{7-24} aralkyl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g, or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, optionally substituted by halogen, hydroxy or carbon

based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, halo substituted C_{1-6} alkyl up to per halo alkyl, halo substituted C_6-C_{12} aryl up to per halo aryl, halo substituted C_3-C_{12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -$C(O)R_g$, or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -$C(O)R_g$,

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO_2R^7, -$C(O)NR^7R^7$, -$C(O)$-R^7, -NO_2, -OR^7, -SR^7, -NR^7R^7, -$NR^7C(O)OR^7$, -$NR^7C(O)R^7$, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7 -C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO_2R^7, -$C(O)R^7$, -$C(O)NR^7R^7$, -OR^7, -SR^7, -NR^7R^7, -NO_2, -$NR^7C(O)R^7$, -$NR^7C(O)OR^7$

and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R^7)-, -$(CH_2)_m$-, -C(O)-, -CH(OH)-, -$(CH_2)_m$O-, -$(CH_2)_m$S-, -$(CH_2)_m$N(R^7)-, -O$(CH_2)_m$- CHX^a-, -CX^a_2-, -S-$(CH_2)_m$- and -N(R^7)$(CH_2)_m$-, where m= 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO_2R^7, -C(O)R^7, -C(O)NR^7R^7, -NO_2, -OR^7, - SR^7 -NR^7R^7, -NR^7C(O)OR^7, -NR^7C(O)R^7, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which is C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_6-C_{14} aryl, or C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO_2R^7, -COR^7, -C(O)NR^7R^7, -OR^7, -SR^7, -NO_2, -NR^7R^7, -NR^7C(O)R^7, and -NR^7C(O)OR^7, with R^7 as defined above

where R_g is $C_{1\text{-}10}$ alkyl; -CN, -CO_2R_d, -OR_d, -SR_d, -NO_2, -C(O)R_e, -NR_dR$_e$, -NR_d C(O)OR_e and -NR_d C(O)R_e, and R_d and R_e are independently selected from the group consisting of hydrogen, $C_{1\text{-}10}$, alkyl, $C_{1\text{-}10}$ alkoxy, $C_{3\text{-}10}$ cycloalkyl having 0-3 heteroatoms selected from O, N and S, $C_{6\text{-}12}$ aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7 -C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3 -C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6 -C_{14} aryl, up to per halo substituted C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl.

2. **(Original)** A compound as in claim 1 wherein:

R_y is hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_{7-24} alkaryl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl having 0-3 heteroatoms selected from N, S and O, substituted C_6-C_{14} aryl, substituted C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} alkaryl or substituted C_7-C_{24} aralkyl, where R_y is a substituted group, it is substituted by halogen up to per halo,

R_z is hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatom, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C_{7-24} alkaryl, C_{7-24} aralkyl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_6-C_{14} aryl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from S, N and O, substituted C_{3-12} hetaryl having 1-3 heteroatoms selected from S, N and O, substituted C_{7-24} alkaryl or substituted C_7-C_{24} aralkyl where R_z is a substituted group, it is substituted by halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and -$C(O)R_g$,

R_a and R_b are,

a) independently hydrogen,

a carbon based moiety selected from the group consisting of C_1 -C_{10} alkyl, C_1-C_{10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from O, N and S, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, C_7-C_{24} alkaryl, substituted C_{1-10} alkyl, substituted C_{1-10} alkoxy, substituted C_{3-10} cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C_{6-12} aryl, substituted C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C_{7-24} aralkyl, substituted C_{7-24} alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12}

halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo heteraryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and -C(O)R_g; or

-OSi(R_f)$_3$ where R_f is hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{6-12} aryl, C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, S and N, C_{7-24} aralkyl, substituted C_{1-10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_3-C_{12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, substituted C_3-C_{12} heteraryl having 1-3 heteroatoms selected from O, S, and N, substituted C_{6-12} aryl, and substituted C_{7-24} alkaryl, where R_f is a substituted group it is substituted halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo heteraryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and -C(O)R_g,

or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, halo substituted C_{1-6} alkyl up to per halo alkyl, halo substituted C_6-C_{12} aryl up to per halo aryl, halo substituted C_3-C_{12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo heteraryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and -C(O)R_g,

or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members,

wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo heteraryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and -$C(O)R_g$,

where R_g is C_{1-10} alkyl; -CN, -CO_2R_d, -OR_d, -SR_d, -NO_2, -$C(O)R_e$, -NR_dR_e, -NR_d $C(O)OR_e$ and -NR_d $C(O)R_e$, and R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-10}, alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_{6-12} aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7 -C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3 -C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6 -C_{14} aryl, up to per halo substituted C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl,

W is independently selected from the group consisting of -CN, -CO_2R^7, -$C(O)NR^7R^7$, -$C(O)$-R^7, -NO_2, -OR^7, -SR^7, -NR^7R^7, -$NR^7C(O)OR^7$, -$NR^7C(O)R^7$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7 -C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C_1-C_{10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkenoyl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C_6-C_{12} aryl, substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N and S, substituted C_7-C_{24} aralkyl, substituted C_7-C_{24} alkaryl, substituted C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and -Q-Ar;

R^7 is independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, up to per-

halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_6-C_{14} aryl, up to per-halosubstituted C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C_7-C_{24} aralkyl, up to per-halosubstituted C_7-C_{24} alkaryl, and up to per-halosubstituted C_4-C_{23} alkheteroaryl; and

each Z is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, - SR^7 $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C_1-C_{10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkenoyl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C_6-C_{12} aryl, substituted C_7-C_{24} alkaryl, substituted C_7-C_{24} aralkyl and substituted C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S; wherein if Z is a substituted group, the one or more substituents are selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$.

3. **(Previously Presented)** A compound as in claim 1 wherein M is -O- .

4. **(Currently Amended)** A compound as in claim 1 wherein the cyclic structures of B and L bound directly to D have hydrogen substituents in the ortho position ~~are not substituted in the ortho position by -OH~~.

5. **(Cancelled)**

6. **(Cancelled)**

7. **(Previously Presented)** A compound of claim 1 wherein B of Formula I is an unsubstituted phenyl group.

8. **(Previously Presented)** A compound of claim 1 wherein B of Formula I is a substituted phenyl group, substituted 1 to 3 times by 1 or more substituents selected from the group consisting of -CN, halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, -OH, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkoxy or phenyl substituted by halogen up to per halo.

9. **(Cancelled)**

10. **(Previously presented)** A compound of claim 8, wherein L, the 6 member cyclic structure bound directly to D, is an unsubstituted phenyl group.

11. **(Cancelled)**

12. **(Previously Presented)** A compound of claim 1, wherein said substituted cyclic moiety L^1 is pyridinyl.

13. **(Previously Presented)** A compound of claim 3, wherein said substituted cyclic moiety L^1 is pyridinyl.

14. **(Previously Presented)** A compound of claim 7, wherein said substituted cyclic moiety L^1 is pyridinyl.

15. **(Previously Presented)** A compound of claim 8, wherein said substituted cyclic moiety L^1 is pyridinyl.

16. **(Cancelled)**

17. **(Previously Presented)** A compound of claim 10, wherein said substituted cyclic moiety L^1 is pyridinyl.

18. **(Previously Presented)** A compound of claim 14, wherein M is -O-.

19. **(Previously Presented)** A compound of claim 15, wherein M is -O-.

20. **(Cancelled)**

21. **(Previously Presented)** A compound of claim 17, wherein M is -O- .

22. **(Original)** A compound of claim 1 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkyl, -CN, -OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

23. **(Original)** A compound of claim 13 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkyl, -CN, -OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

24. **(Original)** A compound of claim 18 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkyl, -CN, -OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

25. **(Original)** A compound of claim 19 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkyl, -CN, -OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

26. **(Cancelled)**

27. **(Original)** A compound of claim 21 wherein L^1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkyl, -CN, -OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

28. **(Cancelled)**

29. **(Cancelled)**

30. **(Original)** A compound of claim 1 wherein L^1 is substituted only by $-C(O)R_x$.

31. **(Cancelled)**

32. **(Cancelled)**

33. **(Previously Presented)** A compound of claim 13 wherein L^1 is substituted by $-C(O)R_x$ wherein R_x is NR_aR_b.

34. **(Previously Presented)** A compound of claim 18 wherein L^1 is substituted by $-C(O)R_x$ wherein R_x is NR_aR_b.

35. **(Previously Presented)** A compound of claim 19 wherein L^1 is substituted by $-C(O)R_x$, wherein R_x is NR_aR_b.

36. **(Cancelled)**

37. **(Previously Presented)** A compound of claim 21 wherein L^1 is substituted by $-C(O)R_x$ wherein R_x is NR_aR_b.

38. **(Previously Presented)** A compound of Formula I:

$$A - D - B \qquad (I)$$

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L^1)$_q$, where L is a 6 membered aryl moiety which is unsubstituted phenyl bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members which is phenyl or pyridinyl, M is -O- and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D which is phenyl or pyridinyl

wherein L^1 is substituted by -C(O)R_x

R_x is NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is of C_1 -C_{10} alkyl, C_1-C_{10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from O, N and S, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl or C_7-C_{24} alkaryl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g or

-OSi(R_f)$_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per

halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g, or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, halo substituted C_{1-6} alkyl up to per halo alkyl, halo substituted C_6-C_{12} aryl up to per halo aryl, halo substituted C_3-C_{12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g, or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g, and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO_2R^7, -C(O)NR^7R^7, -C(O)-R^7, -NO_2, -OR^7, -SR^7, -NR^7R^7, -$NR^7C(O)OR^7$, -$NR^7C(O)R^7$, -Q-Ar, and

carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7 -C_{24} aralkyl, or C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by halogen,

wherein Q is -O-, -S-, $-N(R^7)-$, $-(CH_2)_m-$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$ CHX^a-, $-CX^a{}_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where m= 1-3, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, - SR^7 $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which is C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents are selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$, with R^7 as defined above~~; and~~ where R_g is $C_{1\text{-}10}$ alkyl; -CN, $-CO_2R_d$, $-OR_d$, $-SR_d$, $-NO_2$, $-C(O)R_e$, $-NR_dR_e$, $-NR_d C(O)OR_e$ and $-NR_d C(O)R_e$, and R_d and R_e are independently selected from the group consisting of hydrogen, $C_{1\text{-}10}$, alkyl, $C_{1\text{-}10}$ alkoxy, $C_{3\text{-}10}$ cycloalkyl having 0-3 heteroatoms selected from O, N and S, $C_{6\text{-}12}$ aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7 -

C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3 -C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6 -C_{14} aryl, up to per halo substituted C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or up to per halo substituted C_7-C_{24} aralkyl.

39. (Previously Presented) A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L^1)$_q$, where L is a substituted or unsubstituted phenyl or pyridinyl moiety bound directly to D, L^1 comprises a substituted phenyl, or pyridinyl moiety, M is -O- and

B is a substituted or unsubstituted phenyl group bound directly to D,

wherein L^1 is substituted by-C(O)R_x,

R_x is NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_1 -C_{10} alkyl, C_1-C_{10} alkoxy, $C_{3\text{-}10}$ cycloalkyl, $C_{2\text{-}10}$ alkenyl, $C_{1\text{-}10}$ alkenoyl, $C_{6\text{-}12}$ aryl, $C_{3\text{-}12}$ hetaryl having 1-3 heteroatoms selected from O, N and S, $C_{3\text{-}12}$ cycloalkyl having 0-3 heteroatoms selected from N, S and O, $C_{7\text{-}24}$ aralkyl, or C_7-C_{24} alkaryl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are $C_{1\text{-}10}$ alkyl, $C_{3\text{-}12}$ cycloalkyl having 0-3 heteroatoms selected from O, S and N, $C_{3\text{-}12}$ hetaryl having 1-3 heteroatoms selected from N, S and O, $C_{1\text{-}10}$ alkoxy, $C_{6\text{-}12}$ aryl, $C_{1\text{-}6}$ halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, or halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and -C(O)R_g, or

-OSi(R_f)$_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O, which is $C_{1\text{-}10}$ alkyl, $C_{1\text{-}10}$

alkoxy, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{6-12} aryl, orC_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, S and N, C_{7-24} aralkyl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, or halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and -C(O)R_g, or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, optionally substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, halo substituted C_{1-6} alkyl up to per halo alkyl, halo substituted C_6-C_{12} aryl up to per halo aryl, halo substituted C_3-C_{12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g, or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per

halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or $-C(O)R_g$,

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7 -C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S,

wherein Q is -O-, -S-, $-N(R^7)-$, $-(CH_2)_m-$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$ CHX^a-, $-CX^a{}_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where m= 1-3, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, - SR^7 $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which is C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, or C_4-C_{23} alkheteroaryl having 1-3

heteroatoms selected from O, N and S, and optionally substituted by one or more substituents selected from the group consisting of -CN, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$; and where R_g is C_{1-10} alkyl; -CN, $-CO_2R_d$, $-OR_d$, $-SR_d$, $-NO_2$, $-C(O)R_e$, $-NR_dR_e$, $-NR_d C(O)OR_e$ and $-NR_d C(O)R_e$, and R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-10}, alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_{6-12} aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7 -C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3 -C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6 -C_{14} aryl, up to per halo substituted C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or up to per halo substituted C_7-C_{24} aralkyl.

40. (Currently Amended) A compound as in claim 38 wherein the cyclic structures of B and L bound directly to D have hydrogen substituents in the ortho position ~~are not substituted in the ortho position by OH~~ .

41. (Cancelled)

42. (Currently Amended) A compound as in claim 39 wherein the cyclic structures of B and L bound directly to D have hydrogen substituents in the ortho position ~~are not substituted in the ortho position by OH~~.

43. (Cancelled)

44. (Original) A compound as in claim 38 wherein substituents for B and L and additional substituents for L^1, are selected from the group consisting of C_1-C_{10} alkyl up to per halo substituted C_1-C_{10} alkyl, CN, OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

45. (Original) A compound as in claim 39 wherein substituents for B and L and additional substituents for L^1, are selected from the group consisting of C_1-C_{10} alkyl up to per

halo substituted C_1-C_{10} alkyl, CN, OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

46. (Cancelled)

47. (Cancelled)

48. (Previously Presented) A compound of claim 38 wherein R_a and R_b are independently hydrogen and C_{1-6} alkyl .

49. (Previously Presented) A compound of claim 39 wherein ~~and~~ R_a and R_b are independently hydrogen and C_{1-6} alkyl, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen.

50. (Previously Presented) A pharmaceutically acceptable salt of a compound of formula I of claim 1 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

51. (Previously Presented) A pharmaceutically acceptable salt of a compound of claim 61 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

52. (Previously Presented) A pharmaceutically acceptable salt of a compound of claim 33 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

53. (Previously Presented) A pharmaceutically acceptable salt of a compound of claim 38 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

54. (Previously Presented) A pharmaceutically acceptable salt of a compound of claim 39 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

55. (Original) A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt of a compound of formula I, and a physiologically acceptable carrier.

56. (Previously Presented) A pharmaceutical composition comprising a compound of claim 2 and a physiologically acceptable carrier.

57. (Previously Presented) A pharmaceutical composition comprising a compound of claim 33 and a physiologically acceptable carrier.

58. (Previously Presented) A pharmaceutical composition comprising a compound of claim 38 and a physiologically acceptable carrier.

59. (Previously Presented) A pharmaceutical composition comprising a compound of claim 39 and a physiologically acceptable carrier.

60. **(Cancelled)**

61. **(Currently Amended)** A compound selected from the group consisting of

N-(3-*tert*-butylphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl urea;

N-(3-*tert*-butylphenyl)-*N'*-(4-(4-acetylphenoxy)phenyl urea;

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1,3-dioxoisoindolin-5-yloxy)phenyl) urea[,];

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1-oxoisoindolin-5-yloxy)phenyl) urea[,];

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea[,];

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea[,];

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea[,];

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea[,];

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea;

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea[,];
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea[,];
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea; and
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea.

62. **(Previously Presented)** A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administering a compound of claim 1.

63. **(Previously Presented)** A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administering a compound of claim 33.

64. **(Previously Presented)** A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administering a compound of claim 38.

65. **(Previously Presented)** A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administering a compound of claim 39.

66. **(Cancelled)**

67. **(Currently Amended)** A method for the treatment of a cancerous cell growth mediated by raf kinase, comprising administrating a compound selected from the group consisting of

N-(3-*tert*-butylphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl urea;

N-(3-*tert*-butylphenyl)-*N'*-(4-(4-acetylphenoxy)phenyl urea;

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1,3-dioxoisoindolin-5-yloxy)phenyl) urea[,];

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1-oxoisoindolin-5-yloxy)phenyl) urea[,];

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea;

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea ~~and~~

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea;

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea; and

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea.

68. (Previously Presented) A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of the formula:

-L-M-L^1,

wherein L is

phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl up to perhalo, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy up to per haloalkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

L^1 comprises a substituted cyclic moiety which is

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^7, OR^7, $NR^7R^{7'}$, $C(O)R^7$, $C(O)OR^7$, $C(O)NR^7R^{7'}$, $NR^7C(O)R^{7'}$, $NR^7C(O)OR^{7'}$, halogen, cyano and nitro;

(ii) pyridinyl optionally substituted with 1-3 substituents independently selected from the group consisting of R^7, OR^7, $NR^7R^{7'}$, $C(O)R^7$, $C(O)OR^7$, $C(O)NR^7R^{7'}$, $NR^7C(O)R^{7'}$,

$NR^7C(O)OR^{7'}$, halogen, cyano and nitro; $C(O)OR^7$, $C(O)NR^7R^{7'}$, $NR^7C(O)R^{7'}$, $NR^7C(O)OR^{7'}$, halogen, cyano and nitro; and

wherein L^1 is substituted by $-C(O)R_x$

wherein R_x is R_z or NR_aR_b and R_a and R_b are

a) independently R_z or $-OSi(R_f)_3$; or

b) combined together to form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, optionally substituted by halogen, hydroxy or R_y; or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L^1 to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and R_y;

M is -O-

B is

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^7, OR^7, $NR^7R^{7'}$, $C(O)R^7$, $C(O)OR^7$, $C(O)NR^7R^{7'}$, $NR^7C(O)R^{7'}$, $NR^7C(O)OR^{7'}$ halogen, cyano, and nitro; or

(ii) pyridinyl optionally substituted with 1-3 substituents independently selected from the group consisting of R^7, OR^7, $NR^7R^{7'}$, $C(O)R^7$, $C(O)OR^7$, $C(O)NR^7R^{7'}$, $NR^7C(O)R^{7'}$, $NR^7C(O)OR^{7'}$, halogen, cyano, and nitro; and

each R^7, $R^{7'}$, R_z and R_f is independently

(a) hydrogen,

(b) C_1-C_6 linear, branched, or cyclic alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, up to perhalo substituted C_1-C_5 linear or branched alkyl, C_1-C_3 alkoxy and hydroxy;

(c) C_1-C_6 alkoxy, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, up to perhalo substituted C_1-C_5 linear or branched alkyl, C_1-C_3 alkoxy, hydroxy and halogen;

(d) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, up to perhalo substituted C_1-C_5 linear or branched alkyl, C_1-C_3 alkoxy, hydroxy and halogen,

(e) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, up to perhalo substituted C_1-C_5 linear or branched alkyl, C_1-C_3 alkoxy, hydroxy and halogen,

(f) C_1-C_3 alkyl-phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, up to perhalo substituted C_1-C_5 linear or branched alkyl, C_1-C_3 alkoxy, hydroxy and halogen; and

(g) up to per–halo substituted C_1-C_5 linear, branched or cyclic alkyl, and where not per-halo substituted, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, up to perhalo substituted C_1-C_5 linear or branched alkyl, C_1-C_3 alkoxy and hydroxy.

69. (Cancelled)

70. (Cancelled)

71. (Cancelled)

72. (Cancelled)

73. (Previously Presented) A compound of claim 68 wherein the substituents of the substituted structures of L are selected from the group consisting of methyl, triflouromethyl, ethyl, n-propyl, n-butyl, n-pentyl, i-propyl, t-butyl, methoxy, ethoxy, propoxy, Cl, Br, F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino.

74. (Previously Presented) A compound of claim 68 wherein the substituents of the substituted structures of B and L^1 are independently selected from the group consisting of methyl, triflouromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, *tert*-butyl, sec-butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br and F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino.

75. (Cancelled)

76. (Previously Presented) A compound as in claim 68 wherein B, L and L^1 follow one of the following of combinations:

B= phenyl, L=phenyl and L^1 is phenyl,

B= phenyl, L=phenyl and L^1 is pyridinyl,

B=pyridinyl, L= phenyl and L^1 is phenyl,

B=pyridinyl, L=phenyl and L^1 is pyridinyl,

77. (Previously Presented) A pharmaceutical composition for the treatment of a cancerous cell growth comprising a compound of claim 68 or a pharmaceutically acceptable salt of a compound of formula I and a physiologically acceptable carrier.

78. (Cancelled)

79. (Cancelled)

80. (Previously Presented) A pharmaceutical composition for the treatment of a cancerous cell growth as in claim 77 wherein the pharmaceutically acceptable salt is

a) a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

81. (Cancelled)

82. (Cancelled)

83. (Currently Amended) A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L^1)$_q$, where L is a 6 membered cyclic structure, which is substituted phenyl or unsubstituted phenyl, bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members which is phenyl or pyridinyl,

M is one or more bridging groups selected from the group consisting of -O-, -S-, = $\underline{NR^7}$- ~~-N(R^7)-~~ where R^7 is hydrogen, q is an integer of from 1-3; and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D which is phenyl or pyridinyl,

wherein L^1 is substituted by $-S(O)_2R_x$,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatom, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C_{7-24} alkaryl, C_{7-24} or aralkyl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_1 -C_{10} alkyl, C_1-C_{10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from O, N and S, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, C_{7-24} aralkyl, or C_7-C_{24} alkaryl, and is optionally substituted by halogen, hydroxy and carbon

based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g and are optionally substituted by halogen, or

-OSi(R_f)$_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_{1-10} alkyl, C_{1-10} alkoxy, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{6-12} aryl, C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, S and N, or C_{7-24} aralkyl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g, or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, optionally substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, halo substituted C_{1-6} alkyl up to per halo alkyl, halo substituted C_6-C_{12} aryl up to per halo aryl, halo substituted C_3-C_{12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g, or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g,

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO_2R^7, -C(O)NR^7R^7, -C(O)-R^7, -NO_2, -OR^7, -SR^7, -NR^7R^7, -$NR^7C(O)OR^7$, -$NR^7C(O)R^7$, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7 -C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO_2R^7, -C(O)R^7, -C(O)NR^7R^7, -OR^7, -SR^7, -NR^7R^7, -NO_2, -$NR^7C(O)R^7$, -$NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R^7)-, -$(CH_2)_m$-, -C(O)-, -CH(OH)-, -$(CH_2)_m$O-, -$(CH_2)_m$S-, -$(CH_2)_m$N(R^7)-, -O$(CH_2)_m$- CHX^a-, -CX^a_2-, -S-$(CH_2)_m$- and -N(R^7)$(CH_2)_m$-, where m= 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO_2R^7, -C(O)R^7, -C(O)NR^7R^7, -NO_2, -OR^7, - SR^7 -NR^7R^7, -NR^7C(O)OR^7, -NR^7C(O)R^7, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which is C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_6-C_{14} aryl, or C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO_2R^7, -COR^7, -C(O)NR^7R^7, -OR^7, -SR^7, -NO_2, -NR^7R^7, -NR^7C(O)R^7, and -NR^7C(O)OR^7, with R^7 as defined above,

where R_g is C_{1-10} alkyl; -CN, -CO_2R_d, -OR_d, -SR_d, -NO_2, -C(O)R_e, -N$R_d R_e$, -NR_d C(O)OR_e and -NR_d C(O)R_e, and R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-10}, alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_{6-12} aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7 -C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3 -C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6 -C_{14} aryl, up to per halo substituted C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl.

84. (Currently Amended) A compound of Formula I:

A - D - B (I)

or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L^1)$_q$, where L is a 6 membered cyclic structure, which is substituted phenyl or unsubstituted

phenyl, bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members which is phenyl or pyridinyl,

M is one or more bridging groups selected from the group consisting of -O-, -S-, and -NR^7- ~~-N(R^7)-~~ wherein R^7 is hydrogen, q is an integer of from 1-3; and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D which is phenyl or pyridinyl,

wherein L^1 is substituted by -$C(NR_y)R_z$,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatom, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C_{7-24} alkaryl, C_{7-24} or aralkyl, and optionally substituted by halogen or hydroxy;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatom, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C_{7-24} alkaryl, C_{7-24} or aralkyl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from O, N and S, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -$C(O)R_g$;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_1 -C_{10} alkyl, C_1-C_{10} alkoxy, C_{3-10} cycloalkyl, C_{2-10} alkenyl, C_{1-10} alkenoyl, C_{6-12} aryl, C_{3-12} hetaryl having 1-3 heteroatoms selected from O, N and S, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from N, S and O,

C_{7-24} aralkyl, or C_7-C_{24} alkaryl, and is optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or $-C(O)R_g$ and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O, which is C_{1-10} alkyl, C_{1-10} alkoxy, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{6-12} aryl, C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, S and N, or C_{7-24} aralkyl, and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or $-C(O)R_g$, or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, optionally substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, halo substituted C_{1-6} alkyl up to per halo alkyl, halo substituted C_6-C_{12} aryl up to per halo aryl, halo substituted C_3-C_{12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or $-C(O)R_g$, or

c) one of R_a or R_b is -C(O)-, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O, which are C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7 -C_{24} alkaryl, C_7 -C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_6-C_{12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo hetaryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, or -C(O)R_g,

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and Wn, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO_2R^7, -C(O)NR^7R^7, -C(O)-R^7, -NO_2, -OR^7, -SR^7, -NR^7R^7, -$NR^7C(O)OR^7$, -$NR^7C(O)R^7$, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_7-C_{24} alkaryl, C_7 -C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO_2R^7, -C(O)R^7, -C(O)NR^7R^7, -OR^7, -SR^7, -NR^7R^7, -NO_2, -$NR^7C(O)R^7$, -$NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which are C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_6-C_{14} aryl, C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, C_7-C_{14} alkaryl, C_7-C_{24} aralkyl, or C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R^7)-, -$(CH_2)_m$-, -C(O)-, -CH(OH)-, -$(CH_2)_m$O-, -$(CH_2)_m$S-, -$(CH_2)_m$N(R^7)-, -O$(CH_2)_m$- CHX^a-, -CX^a_2-, -S-$(CH_2)_m$- and -N(R^7)$(CH_2)_m$-, where m= 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO_2R^7, -C(O)R^7, -C(O)NR^7R^7, -NO_2, -OR^7, - SR^7 -NR^7R^7, -NR^7C(O)OR^7, -NR^7C(O)R^7, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O, which is C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_6-C_{14} aryl, or C_3-C_{13} hetaryl having 1-3 heteroatoms selected from O, N and S, and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO_2R^7, -COR^7, -C(O)NR^7R^7, -OR^7, -SR^7, -NO_2, -NR^7R^7, -NR^7C(O)R^7, and -NR^7C(O)OR^7, with R^7 as defined above,

where R_g is C_{1-10} alkyl; -CN, -CO_2R_d, -OR_d, -SR_d, -NO_2, -C(O)R_e, -N$R_d R_e$, -NR_d C(O)OR_e and -NR_d C(O)R_e, and R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-10}, alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_{6-12} aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7 -C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3 -C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6 -C_{14} aryl, up to per halo substituted C_3 -C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl.

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. **(Currently Amended)** A method for treating a disease in a human or other mammal mediated by a VEGF-induced signal transduction pathway, wherein the disease that is treated is one or more of the following conditions: retinopathy and retinopathy of prematurity, comprising administering to a human or other mammal in need thereof a compound of Formula I, a salt form of a compound of Formula I, an isomer of a compound of Formula I or a prodrug of a compound of Formula I to regulate a VEGF-mediated signal transduction cascade,

A-NH-C(O)-NH-B I

wherein A is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(iii) 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro; and

(iv) 10 membered bicyclic heteroaryl groups in which the first ring is bonded to the NH of Figure I and contains 1-3 heteroatoms independently selected from the group consisting of O, N, and S, and the second ring is fused to the first ring using 3 to 4 carbon atoms, the bicyclic heteroaryl group is optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro,

B is selected from the group consisting of

(i) phenyl, substituted with 1-2 substituents independently selected from the group consisting of -L-M, optionally substituted with C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

(ii) naphthyl, substituted with 1-2 substituents independently selected from the group consisting of -L-M, optionally substituted with C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

(iii) 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, substituted with 1-2 substituents independently selected from the group consisting of -L-M, optionally substituted with C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

(iv) 10 membered bicyclic heteroaryl groups having 1-6 heteroatoms independently selected from the group consisting of O, N and S, substituted with 1-2 substituents independently selected from the group consisting of -L-M, optionally substituted

with C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

L is selected from the group consisting of:

(a) $-(CH_2)_m-O-(CH_2)_l-$,

(b) $-(CH_2)_m-(CH_2)_l-$,

(c) $-(CH_2)_m-C(O)-(CH_2)_l-$,

(d) $-(CH_2)_m-NR^3-(CH_2)_l-$,

(e) $-(CH_2)_m-NR^3C(O)-(CH_2)_l-$,

(f) $-(CH_2)_m-S-(CH_2)_l-$,

(g) $-(CH_2)_m-C(O)NR^3-(CH_2)_l-$,

(h) $-(CH_2)_m-CF_2-(CH_2)_l-$,

(i) $-(CH_2)_m-CCl_2-(CH_2)_l-$,

(j) $-(CH_2)_m-CHF-(CH_2)_l-$,

(k) $-(CH_2)_m-CH(OH)-(CH_2)_l-$;

(l) $-(CH_2)_m-C\equiv C-(CH_2)_l-$;

(m) ~~$-(CH_2)_m-C=C-(CH_2)_l-$~~ $-(CH_2)_m-CH=CH-(CH_2)_l-$; and

(n) $-(CH_2)_m-CR^4R^5-(CH_2)_l-$;

wherein the variables m and l are integers independently selected from 0-4,

M is selected from the group consisting of :

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(iii) 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro and ~~also~~ oxides ~~(e.g. =O, O^- or OH)~~; ~~and~~

(iv) 10 membered bicyclic heteroaryl groups, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro and ~~also~~ oxides ~~(e.g. =O, O^- or OH)~~;

(v) saturated and partially saturated C_3-C_6 monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and[[,]] nitro;

(vi) saturated and partially saturated C_8-C_{10} bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(vii) saturated and partially saturated 5 and 6 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group

consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro, and ~~also~~ oxides ~~(e.g. =O, -O⁻ or -OH)~~; and

(viii) saturated and partially saturated 8 to 10 membered bicyclic heterocyclic moiety, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro, and ~~also~~ oxides ~~(e.g. =O, -O⁻ or -OH)~~;

wherein each R^1 - R^5 is independently selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6 alkyl, ~~preferably, C_1-C_5 linear, branched, or cyclic alkyl,~~ wherein said alkyl is optionally substituted with halogen up to per-halo;

(c) phenyl;

(d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S;

(e) C_1-C_3 alkyl-phenyl wherein said alkyl moiety is optionally substituted with halogen up to per-halo; and

(f) C_1-C_3 alkyl-heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, and wherein said alkyl moiety is optionally substituted with halogen up to per-halo,

wherein each R^1 - R^5, when not hydrogen is optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear branched or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo, C_1-C_3 alkoxy, wherein said alkoxy is optionally substituted with halogen up to per-halo, hydroxy, amino, C_1-C_3 alkylamino, C_2-C_6 dialkylamino, halogen, cyano, and nitro;

each variable q is independently selected from 0, 1, or 2; and

wherein A, B and M of formula I follow one of the following combinations:

A= phenyl, B=phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= phenyl, B=pyridinyl and M is pyridinyl, quinolinyl, isoquinolinyl or not present,

A=phenyl, B = naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=pyridinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A=isoquinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= isoquinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= isoquinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= phenyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present,

A= quinolinyl, B= pyridinyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present, or

A= quinolinyl, B= naphthyl and M is phenyl, pyridinyl, quinolinyl, isoquinolinyl or not present.

2. (Canceled)

3. (Currently Amended) A method as in claim 1 wherein the substituents on the groups for A, B, and M are selected from the group consisting of: methyl, ethyl, propyl, butyl, pentyl, isopropyl, isobutyl, *sec*-butyl, [[and]] *tert*-butyl, F, Cl, Br, and I.

4.—5. (Canceled)

6. (Currently Amended) A method of claim 1 wherein the substituents of the substituted structures of B are each, independently, selected from the group consisting of methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br, [[and]] F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino, diethylamino and the structure -L-M.

7. (Currently Amended) A method of claim 6 wherein the substituents of the substituted structures of A and M are each, independently, selected from the group consisting of

methyl, trifluoromethyl, ethyl, n-propyl, n-butyl, n-pentyl, isopropyl, *tert*-butyl, sec-butyl, isobutyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, Cl, Br, [[and]] F, cyano, nitro, hydroxy, amino, methylamino, dimethylamino, ethylamino and diethylamino and further include:

phenyl, pyridinyl, pyrimidinyl, chlorophenyl, dichlorophenyl, bromophenyl, dibromophenyl, chloropyridinyl, bromopyridinyl, dichloropyridinyl, dibromopyridinyl methylphenyl, methylpyridinyl quinolinyl, isoquinolinyl, isoindolinyl, pyrazinyl, pyridazinyl, pyrrolinyl, imidazolinyl, thienyl, furyl, isoxazolinyl, isothiazolinyl, benzopyridinyl, benzothiazolyl, C_1-C_5 acyl;

NH(C_1-C_5 alkyl, phenyl or pyridinyl)~~, such as aminophenyl~~;

N(C_1-C_5 alkyl)(C_1-C_5 alkyl, phenyl or pyridinyl)~~, such as diethylamino and dimethyl amino~~;

$S(O)_q$ (C_1-C_5 alkyl); ~~such as methanesulfonyl;~~

$S(O)_q$ H;

SO_2NH_2;

$SO_2NH(C_1$-C_5 alkyl);

$SO_2N(C_1$-C_5 alkyl)(C_1-C_5 alkyl);

$NHSO_2(C_1$-C_5 alkyl); $N(C_1$-C_3 alkyl) $SO_2(C_1$-C_5 alkyl);

$CO(C_1$-C_6 alkyl or phenyl);

C(O)H;

C(O)O(C_1-C_6 alkyl or phenyl)~~, such as $C(O)OCH_3$, $C(O)OCH_2CH_3$, $C(O)OCH_2CH_2CH_3$~~;

C(O)OH;

$C(O)NH_2$ (carbamoyl);

C(O)NH(C_1-C_6 alkyl or phenyl)~~, such as N-methylethyl carbamoyl, N-methyl carbamoyl, N-ethylcarbamoyl, or N-dimethylamino ethyl carbamoyl~~;

C(O)N(C_1-C_6 alkyl or phenyl)(C_1-C_6 alkyl, phenyl or pyridinyl)~~, such as N-dimethyl carbamoyl~~;

C(N(C_1-C_5 alkyl)) (C_1-C_5 alkyl);

NHC(O)(C_1-C_6 alkyl or phenyl) and

N(C_1-C_5 alkyl[[,]])C(O)(C_1-C_5 alkyl).

wherein each of the above substituents is optionally partially or fully halogenated.

8. (Previously Presented) A method as in claim 1 wherein A and M of formula I are independently selected from the group consisting of substituted or unsubstituted phenyl and pyridinyl.

9. (Previously Presented) A method as in claim 8 wherein B of formula I is a phenyl group, optionally substituted by halogen up to per halo and 0 to 3 times by one or more substituents selected from the group consisting of -CN, C_1-C_5 alkyl, C_1-C_5 alkoxy, -OH, phenyl, up to per halo substituted C_1-C_5 alkyl, up to per halo substituted C_1-C_5 alkoxy and up to per halo substituted phenyl.

10. (Canceled)

11. (Currently Amended) A method as in claim 1 wherein L of formula I is -O-, -S-, -NH-, -N(CH_3)-, -NHCH_2-, -NC_2H_4-, -CH_2-, -C(O)-, -CH(OH)-, -NHC(O)N(CH_3)CH_2-, -N(CH_3)C(O)N(CH_3)CH_2-, -CH_2C(O)N(CH_3)-, -C(O)N(CH_3)CH_2-,

-NHC(O)-, -N(CH_3)C(O)-, -C(O)N(CH_3)-, -C(O)NH-, -CH_2O-, -CH_2S-, -CH_2N(CH_3)-, -OCH_2-, -CHF-, -CF_2-,-CCl_2-, -S-CH_2-, or ~~and~~ -N(CH_3)CH_2 -.

12.—17. (Canceled)

18. (Currently Amended) A method for treating a disease in a human or other mammal mediated by a VEGF-induced signal transduction pathway, wherein the disease that is treated is one or more of the following conditions: retinopathy and retinopathy of prematurity, comprising administering to a human or other mammal in need thereof a compound of Formula I, a salt form of a compound of Formula I, an isomer of a compound of Formula I or a prodrug of a compound of Formula I to regulate a VEGF-mediated signal transduction cascade,

A-NH-C(O)-NH-B I

wherein A is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro; and

(iv) 8 to 10 membered bicyclic heteroaryl groups in which the first ring is bonded to the NH of Figure I and contains 1-3 heteroatoms independently selected from the group consisting of O, N, and S, and the second ring is fused to the first ring using 3 to 4 carbon atoms, the bicyclic heteroaryl group is optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro,

B is selected from the group consisting of

(i) phenyl, substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

(ii) naphthyl, substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro; and

(iv) 8 to 10 membered bicyclic heteroaryl groups having 1-6 heteroatoms independently selected from the group consisting of O, N and S, substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or

branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

L is selected from the group consisting of:

(a) $-(CH_2)_m-O-(CH_2)_l-$,

(b) $-(CH_2)_m-(CH_2)_l-$,

(c) $-(CH_2)_m-C(O)-(CH_2)_l-$,

(d) $-(CH_2)_m-NR^3-(CH_2)_l-$,

(e) $-(CH_2)_m- NR^3C(O)-(CH_2)_l-$,

(f) $-(CH_2)_m-S-(CH_2)_l-$,

(g) $-(CH_2)_m-C(O)NR^3-(CH_2)_l-$,

(h) $-(CH_2)_m-CF_2-(CH_2)_l-$,

(i) $-(CH_2)_m-CCl_2-(CH_2)_l-$,

(j) $-(CH_2)_m-CHF-(CH_2)_l-$,

(k) $-(CH_2)_m-CH(OH)-(CH_2)_l-$;

(l) $-(CH_2)_m-C\equiv C-(CH_2)_l-$;

(m) ~~$-(CH_2)_m-C=C-(CH_2)_l-$~~ $-(CH_2)_m-CH=CH-(CH_2)_l-$; and

(n) $-(CH_2)_m-CR^4R^5-(CH_2)_l-$;

wherein the variables m and l are integers independently selected from 0-4,

M is selected from the group consisting of :

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro and ~~also~~ oxides ~~(e.g. =O, -O⁻ or -OH)~~; ~~and~~

(iv) 8 to 10 membered bicyclic heteroaryl groups, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro and ~~also~~ oxides ~~(e.g. =O, -O⁻ or -OH).~~;

(v) saturated and partially saturated C_3-C_6 monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and[[,]] nitro;

(vi) saturated and partially saturated C_8-C_{10} bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(vii) saturated and partially saturated 5 and 6 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group

consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro, and ~~also~~ oxides ~~(e.g. =O, -O⁻ or -OH)~~; and

(viii) saturated and partially saturated 8 to 10 membered bicyclic heterocyclic moiety, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, ~~and~~ nitro, and ~~also~~ oxides ~~(e.g. =O, -O⁻ or -OH)~~;

wherein each R^1 - R^5 is independently selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6 alkyl, ~~preferably, C_1-C_5 linear, branched, or cyclic alkyl,~~ wherein said alkyl is optionally substituted with halogen up to per-halo;

(c) phenyl;

(d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S;

(e) C_1-C_3 alkyl-phenyl wherein said alkyl moiety is optionally substituted with halogen up to per-halo; and

(f) C_1-C_3 alkyl-heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, and wherein said alkyl moiety is optionally substituted with halogen up to per-halo,

wherein each R^1 - R^5, when not hydrogen is optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear branched or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo, C_1-C_3 alkoxy, wherein said alkoxy is optionally substituted with halogen up to per-halo, hydroxy, amino, C_1-C_3 alkylamino, C_2-C_6 dialkylamino, halogen, cyano, and nitro;

each variable q is independently selected from 0, 1, or 2;

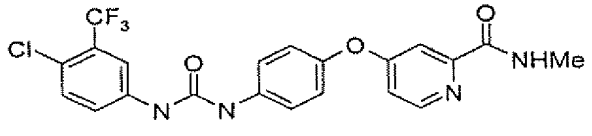
wherein B is substituted by -L-M and

M is substituted by at least one substituent selected from the group consisting of $S(O)_qR^1$, $SO_2NR^1R^2$, $C(O)R^1$, $C(O)OR^1$ and $C(O)NR^1R^2$.

19. (Previously Presented) A method as in claim 18, wherein M is substituted by at least one substituent selected from the group consisting of -$C(O)R^1$, $C(O)OR^1$, and $C(O)NR^1R^2$, wherein R^1 and R^2 are independently as defined in claim 18.

20. (Previously Presented) A method of claim 18 wherein M is substituted by -$C(O)\ NR^1R^2$, wherein R^1 and R^2 are independently as defined in claim 18.

21. (Previously Presented) A method for treating a disease in a human or other mammal mediated by a VEGF-induced signal transduction pathway wherein the disease that is treated is one or more of the following conditions: retinopathy and retinopathy of prematurity, comprising administering to a human or other mammal in need thereof the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea of the formula below or a pharmaceutically acceptable salt thereof to regulate a VEGF-mediated signal transduction cascade,



22. (Previously Presented) A method for treating a disease in a human or other mammal mediated by a VEGF-induced signal transduction pathway wherein the disease that is treated is one or more of the following conditions: retinopathy and retinopathy of prematurity, comprising administering to a human or other mammal in need thereof the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate to regulate a VEGF-mediated signal transduction cascade.

23. (Previously Presented) A method of claim 18 wherein the structures of A, B and M are each, independently selected from the group consisting of phenyl, substituted phenyl, pyridinyl, substituted pyridinyl, pyrimidinyl, substituted pyrimidinyl, naphthyl, substituted naphthyl, isoquinolinyl, substituted isoquinolinyl, quinolinyl and substituted quinolinyl.

24. (Currently Amended) A method as in claim 1, wherein M is substituted by at least one substituent selected from the group consisting of $S(O)_qR^1$, $SO_2NR^1R^2$, $C(O)R^1$, $C(O)OR^1$, and $C(O)NR^1R^2$ wherein q, R^1 and R^2 are independently as defined in claim 1.

25. (Previously Presented) A method of claim 20 wherein M is additionally substituted by one or more substituents selected from the group consisting of C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkyl, -CN, -OH, halogen, C_1-C_{10} alkoxy and up to per halo substituted C_1-C_{10} alkoxy.

26. (Previously Presented) A method as in claim 20 wherein L of formula I is -O-, -S-, -NH-, -$N(CH_3)$-, -$NHCH_2$-, -NC_2H_4-, -CH_2-, -C(O)-, -CH(OH)-, -$NHC(O)N(CH_3)CH_2$-, -$NCH_3C(O)N(CH_3)CH_2$-, -$CH_2C(O)N(CH_3)$-, $C(O)N(CH_3)CH_2$-, -NHC(O)-, -$N(CH_3)C(O)$-, -$C(O)N(CH_3)$-, -C(O)NH-, -CH_2O-, -CH_2S-, -$CH_2N(CH_3)$-, -OCH_2-, -CHF-, -CF_2-,-CCl_2-, -S-CH_2- or -$N(CH_3)CH_2$-.

27. (Original) A method of claim 1 wherein L of formula I is selected from the group consisting of -O-, -S-, -$N(R^{35})$-, -$(CH_2)_m$-, -C(O)-, -CH(OH)-, -$(CH_2)_m$O, where m= 1-3 and R^{35} is hydrogen, C_1-C_{10} alkyl, up to per halo substituted C_1-C_{10} alkyl, -CN, -OH, halogen, C_1-C_{10} alkoxy or up to per halo substituted C_1-C_{10} alkoxy.

28. (Original) A method of claim 1 wherein M is substituted by -$C(O)NR^1R^2$ and R^1 and R^2 are as defined in claim 1.

29. (Previously Presented) A method of claim 18 wherein M is

a saturated C_3-C_6 monocyclic carbocyclic moiety selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, and cyclohexanyl;

a saturated C_8-C_{10} bicyclic carbocyclic moiety selected from the group consisting of bicyclopentanyl and bicyclohexanyl;

a partially saturated C_3-C_6 monocyclic carbocyclic moiety selected from the group consisting of cyclopentenyl, cyclohexenyl and cyclohexadienyl;

the partially saturated C_8-C_{10} bicyclic carbocyclic moiety bicyclohexenyl;

a substituted naphthyl group selected from benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl and tetrahydronaphthyl; or

an 8 to 10 membered bicyclic heteroaryl group selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclcopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridiazine, cyclohexanopyridazine, cyclopentanothiophene and cyclohexanothiophene.

30. (Previously Presented) A method as in claim 1 wherein the disease that is treated is a VEGFR-2 mediated disorder.

31. (Previously Presented) A method as in claim 1 wherein the disease that is treated is a VEGFR-1 mediated disorder.

32. (Canceled)

33. (Previously Presented) A method as in claim 1 wherein the disease that is treated is a VEGFR-3 mediated disorder.

34. (New) A method for treating or preventing a disease in a human or other mammal regulated by tyrosine kinase (associated with an aberration in the tyrosine kinase signal transduction pathway) comprising administering to a human or other mammal in need thereof a compound of Formula I, a salt form of a compound of Formula I, an isomer of a compound of Formula I or a prodrug of a compound of Formula I

A-NH-C(O)-NH-B

I

wherein A is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro; and

(iv) 8 to 10 membered bicyclic heteroaryl group in which the first ring is bonded to the NH of Figure I and contains 1-3 heteroatoms independently selected from the group consisting of O, N, and S, and the second ring is fused to the first ring using 3 to 4 carbon atoms, the bicyclic heteroaryl group is optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, and nitro,

B is selected from the group consisting of

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched

haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro; and

(iv) 8 to 10 membered bicyclic heteroaryl groups having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of -L-M, C_1-C_5 linear or branched alkyl, C_1-C_5 linear or branched haloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro;

L is selected from the group consisting of :

(a) $-(CH_2)_m-O-(CH_2)_l-$,

(b) $-(CH_2)_m-(CH_2)_l-$,

(c) $-(CH_2)_m-C(O)-(CH_2)_l-$,

(d) $-(CH_2)_m-NR^3-(CH_2)_l-$,

(e) $-(CH_2)_m- NR^3C(O)-(CH_2)_l-$,

(f) $-(CH_2)_m-S-(CH_2)_l-$,

(g) $-(CH_2)_m-C(O)NR^3-(CH_2)_l-$,

(h) $-(CH_2)_m-CF_2-(CH_2)_l-$,

(i) $-(CH_2)_m-CCl_2-(CH_2)_l-$,

(j) $-(CH_2)_m-CHF-(CH_2)_l-$,

(k) $-(CH_2)_m-CH(OH)-(CH_2)_l-$;

(l) $-(CH_2)_m-C\equiv C-(CH_2)_l-$;

(m) $-(CH_2)_m-CH=CH-(CH_2)_l-$; and

(n) a single bond, where m and l are 0;

(o) $-(CH_2)_m-CR^4R^5-(CH_2)_l-$;

wherein the variables m and l are integers independently selected from 0-4,

M is selected from the group consisting of :

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(ii) naphthyl, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(iii) 5 and 6 membered monocyclic heteroaryl groups, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, nitro and oxides;

(iv) 8 to 10 membered bicyclic heteroaryl groups, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, nitro and oxides;

(v) saturated and partially saturated C_3-C_6 monocyclic carbocyclic moiety optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(vi) saturated and partially saturated C_8-C_{10} bicyclic carbocyclic moiety, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano and nitro;

(vii) saturated and partially saturated 5 and 6 membered monocyclic heterocyclic moiety, having 1-3 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, nitro, and oxides; and

(viii) saturated and partially saturated 8 to 10 membered bicyclic heterocyclic moiety, having 1-6 heteroatoms independently selected from the group consisting of O, N and S, optionally substituted with 1-3 substituents independently selected from the group

consisting of R^1, OR^1, NR^1R^2, $S(O)_qR^1$, $SO_2NR^1R^2$, $NR^1SO_2R^2$, $C(O)R^1$, $C(O)OR^1$, $C(O)NR^1R^2$, $NR^1C(O)R^2$, $NR^1C(O)OR^2$, halogen, cyano, nitro, and oxides;

wherein each R^1 - R^5 is independently selected from the group consisting of:

(a) hydrogen,

(b) C_1-C_6 alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo;

(c) phenyl;

(d) 5-6 membered monocyclic heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S or 8-10 membered bicyclic heteroaryl having 1-6 heteroatoms selected from the group consisting of O, N and S;

(e) C_1-C_3 alkyl-phenyl wherein said alkyl moiety is optionally substituted with halogen up to per-halo; and

(f) C_1-C_3 alkyl-heteroaryl having 1-4 heteroatoms selected from the group consisting of O, N and S, wherein said heteroaryl group is a 5-6 membered monocyclic heteroaryl or a 8-10 membered bicyclic heteroaryl, and wherein said alkyl moiety is optionally substituted with halogen up to per-halo,

wherein each R^1 - R^5, when not hydrogen is optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear branched or cyclic alkyl, wherein said alkyl is optionally substituted with halogen up to per-halo, C_1-C_3 alkoxy, wherein said alkoxy is optionally substituted with halogen up to per-halo, hydroxy, amino, C_1-C_3 alkylamino, C_2-C_6 dialkylamino, halogen, cyano, and nitro; and

each variable q is independently selected from 0, 1, or 2.

35. (New) A method as in claim 1, wherein the oxides are selected from the group consisting of -O, $-O^-$, and -OH.

36. (New) A method as in claim 1, wherein the C_1-C_6 alkyl of the group for R^1-R^5 is a C_1-C_5 linear, branched or cyclic alkyl.

37. (New) A method as in claim 18, wherein the oxides are selected from the group consisting of -O, $-O^-$, and -OH.

38. (New) A method as in claim 18, wherein the C_1-C_6 alkyl of the group for R^1-R^5 is a C_1-C_5 linear, branched or cyclic alkyl.

Listing of Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1.–73. (Canceled)

74. (Previously Presented) A method for the treatment of a solid tumor in a human or animal comprising administering

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea, or

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

75.–80. (Canceled)

81. (Previously Presented) A method for the treatment of a carcinoma, myeloid disorder or adenoma in a human or animal comprising administering

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea, or

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl.

82.–86. (Canceled)

87. (Previously Presented) A method for the treatment of carcinoma of the lung, pancreas,

thyroid, bladder or colon in a human or animal comprising administering *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea, or *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl.

88.–92. (Canceled)

93. (Previously Presented) A method as in claim 81 for the treatment of myeloid leukemia or villous colon adenoma.

94–98. (Canceled)

99. (Previously Presented) A method of claim 74 wherein a human is treated.

100. (Previously Presented) A method of claim 87 for the treatment of carcinoma of the lung in a human.

101. (Previously Presented) A method of claim 87 for the treatment of carcinoma of the pancreas in a human.

102. (Previously Presented) A method of claim 87 for the treatment of carcinoma of the thyroid in a human.

103. (Previously Presented) A method of claim 87 for the treatment of carcinoma of the bladder in a human.

104. (Previously Presented) A method of claim 87 for the treatment of carcinoma of the colon in a human.

105. (Previously Presented) A method of claim 99 comprising administering *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

106. (Previously Presented) A method for the treatment of a solid tumor in a human or animal comprising administering a tosylate salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea or *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

107. (Previously Presented) A method for the treatment of a carcinoma, myeloid disorder or adenoma in a human or animal comprising administering a tosylate salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea or *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

108. (Previously Presented) A method for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon in a human or animal comprising administering a tosylate salt of *N*-(4-

chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea or *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

109. (Previously Presented) A method as in claim 107 for the treatment of myeloid leukemia or villous colon adenoma.

110. (Previously Presented) A method of claim 106 wherein a human is treated.

111. (Previously Presented) A method of claim 108 for the treatment of carcinoma of the lung in a human.

112. (Previously Presented) A method of claim 108 for the treatment of carcinoma of the pancreas in a human.

113. (Previously Presented) A method of claim 108 for the treatment of carcinoma of the thyroid in a human.

114. (Previously Presented) A method of claim 108 for the treatment of carcinoma of the bladder in a human.

115. (Previously Presented) A method of claim 108 for the treatment of carcinoma of the colon in a human.

116. (Currently Amended) A method of claim 109 comprising administering a tosylate salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

117. (New) A method for inhibiting RAF-kinase in a human or mammal comprising administering a tosylate of salt *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea, or *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

10/042,203

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	:	
Bernd RIEDL et al.	:	Group Art Unit: TO BE ASSIGNED
Serial No.: TO BE ASSIGNED	:	Examiner: TO BE ASSIGNED
Filed: January 11, 2002	:	

For: ω-CARBOXYARYL SUBSTITUTED DIPHENYL UREAS AS RAF KINASE INHIBITORS

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the accompanying application as follows.

IN THE SPECIFICATION

Page 1, line 1, after the title insert

--Priority is claimed to provisional application Serial No. (Unassigned), filed on January 12, 2001.--

IN THE CLAIMS

Please cancel claims 1-49 and 55-67 without prejudice or disclaimer.

Please amend claims 50-59 as follows.

Claim 50. (Amended) A pharmaceutically acceptable salt of claim 69 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid;

and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 51. (Amended) A pharmaceutically acceptable salt of claim 70 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 52. (Amended) A pharmaceutically acceptable salt of claim 71 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 53. (Amended) A pharmaceutically acceptable salt of claim 72 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Claim 54. (Amended) A pharmaceutically acceptable salt of claim 73 selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

Please add new claims 68-109 as follows.

--68. A pharmaceutically acceptable salt of a compound selected from the group consisting of:

N-(5-*tert*-butyl-2-methoxy phenyl)-*N*=-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N*=-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and their pharmaceutically acceptable salts.

69. A pharmaceutically acceptable salt of the compound
N-(5-*tert*-butyl-2-methoxy phenyl)-*N*=-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea.

70. A pharmaceutically acceptable salt of the compound
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

71. A pharmaceutically acceptable salt of the compound
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

72. A pharmaceutically acceptable salt of the compound
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

73. A pharmaceutically acceptable salt of the compound
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N*=-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

74. A method for the treatment of a cancerous cell growth mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of a compound selected from the group consisting of:
N-(5-*tert*-butyl-2-methoxy phenyl)-*N*=-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N*=-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

75. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of *N*-(5-tert-butyl-2-methoxy phenyl)-*N*=-(4-(4-methoxy-3-(*N*-methyl carbamoyl)phenoxy)phenyl) urea.

76. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of *N*-(2-methoxy-5-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

77. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

78. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

79. A method for the treatment of a cancerous cell growth as in claim 74 mediated by RAF kinase comprising administering a pharmaceutically acceptable salt of *N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N*=-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

80. A method as in claim 74 for the treatment of solid cancers.

81. A method as in claim 74 for the treatment of carcinomas, myleoid disorders or adenomas.

82. A method as in claim 75 for the treatment of carcinomas, myleoid disorders or adenomas.

83. A method as in claim 76 for the treatment of carcinomas, myleoid disorders or adenomas.

84. A method as in claim 77 for the treatment of carcinomas, myleoid disorders or adenomas.

85. A method as in claim 78 for the treatment of carcinomas, myleoid disorders or adenomas.

86. A method as in claim 79 for the treatment of carcinomas, myleoid disorders or adenomas.

87. A method as in claim 74 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

88. A method as in claim 75 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

89. A method as in claim 76 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

90. A method as in claim 77 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

91. A method as in claim 78 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

92. A method as in claim 79 for the treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon.

93. A method as in claim 74 for the treatment of myeloid leukemia or villous colon adenomas.

94. A method as in claim 75 for the treatment of myeloid leukemia or villous colon adenomas.

95. A method as in claim 76 for the treatment of myeloid leukemia or villous colon adenomas.

96. A method as in claim 77 for the treatment of myeloid leukemia or villous colon adenomas.

97. A method as in claim 78 for the treatment of myeloid leukemia or villous colon adenomas.

98. A method as in claim 79 for the treatment of myeloid leukemia or villous colon adenomas.

99. A method as in claim 74 wherein the pharmaceutically acceptable salt administered is selected from the group of salts consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

100. A method as in claim 75 where the pharmaceutical acceptable salt administered is the tosylate salt of
N-(5-tert-butyl-2-methoxy phenyl)-*N*=-(4-(4-methoxy-3-(*N*-methyl carbamoyl)phenoxy)phenyl) urea.

101. A method as in claim 76 where the pharmaceutical acceptable salt administered is the tosylate salt of
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

102. A method as in claim 77 where the pharmaceutical acceptable salt administered is the tosylate salt of
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

103. A method as in claim 78 where the pharmaceutical acceptable salt administered is the tosylate salt of
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

104. A method as in claim 79 where the pharmaceutical acceptable salt administered is the tosylate salt of
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N*=-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

105. A pharmaceutical acceptable salt as in claim 69 which is the tosylate salt of
N-(5-*tert*-butyl-2-methoxy phenyl)-*N*=-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea.

106. A pharmaceutical acceptable salt as in claim 70 which is the tosylate salt of
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

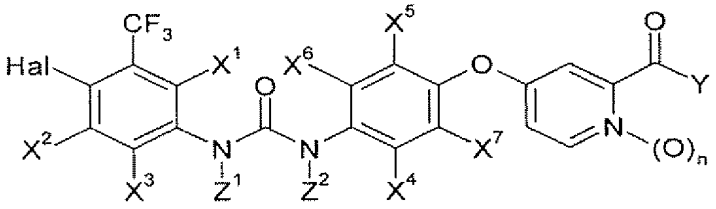
107. A pharmaceutical acceptable salt as in claim 71 which is the tosylate salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea.

108. A pharmaceutical acceptable salt as in claim 72 which is the tosylate salt of *N*-(4-chloro-3-(trifluoromethyl)phenyl)-*N*=-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

109. A pharmaceutical acceptable salt as in claim 73 which is the tosylate salt of *N*-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N*=-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.--

(viii) Claims Appendix

1. **(Previously Presented)** A compound of formula (I),



(I)

wherein,

Y	is OR^1 or NHR^2,
Hal	is chlorine or bromine,
R^1	is H or C_1-C_6 alkyl,
R^2	is H, OH, CH_3 or CH_2OH,
Z^1 and Z^2	are each H or OH, wherein only one of Z^1 or Z^2 can be OH,
X^1 to X^7	are each, independently, H, OH or $O(CO)C_1$-C_4 alkyl, and
n	is 0 or 1,

with the proviso that at least one of conditions a-c is met,

a) Z^1 or Z^2 is OH,

b) Y is NHR^2 and R^2 is OH,

c) n is 1,

or a salt thereof, or an isolated stereoisomer thereof.

2. **(Original)** A compound of claim 1 wherein n of formula I is 1.

3. **(Original)** A compound of claim 2 wherein Y is NHR^2 and R^2 is H or CH_3,

4. **(Original)** A compound of claim 2 wherein

a) X^1 to X^7 are each H, or

b) Z^1 and Z^2 are each H.

5. **(Original)** A compound of claim 2 wherein

a) X^1 to X^7 are each H, or

b) Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H, or

c) X^1 to X^7 and Z^1 are each H and Z^2 is OH or

d) X^1 to X^7 and Z^2 are each H and Z^1 is OH.

6. **(Original)** A compound of claim 2, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl.

7. **(Original)** A compound of claim 2, wherein Y is NHR^2 and R^2 is CH_2OH or OH.

8. **(Original)** A compound of claim 2 wherein Y is OH.

9. **(Original)** A compound of claim 1, wherein Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H.

10. **(Original)** A compound of claim 9, wherein n is 0.

11. **(Original)** A compound of claim 10, wherein R^2 is H or CH_3.

12. **(Original)** A compound of claim 10, wherein X^1 to X^7 are each H.

13. **(Original)** A compound of claim 10, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl.

14. **(Original)** A compound of claim 10, wherein R^2 is CH_2OH or OH.

15. **(Original)** A compound of claim 10, wherein Y is OH.

16. **(Original)** A compound of claim 1, wherein in formula (I), Y is NHR^2 and R^2 is OH.

17. **(Original)** A compound of claim 16, wherein n is 0.

18. **(Previously Presented)** A compound of claim 17, wherein X^1 to X^7 are each H.

19. **(Original)** A compound of claim 17, wherein Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H.

20. (Original) A compound of claim 17, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl.

21. (Original) A compound of claim 1, wherein in formula (I), Y is OH.

22. (Original) A compound of claim 21, wherein n is 0.

23. (Original) A compound of claim 22, wherein X^1 to X^7 are each H.

24. (Original) A compound of claim 22, wherein Z^2 is H and Z^1 is OH.

25. (Original) A compound of claim 22, wherein Z^1 is H and Z^2 is OH.

26. (Original) A compound of claim 22, wherein at least one of X^1 to X^7 is OH or $O(CO)C_1$-C_4 alkyl.

27. (Original) A compound selected from the group consisting of :

4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,

4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridine carboxamide 1-oxide,

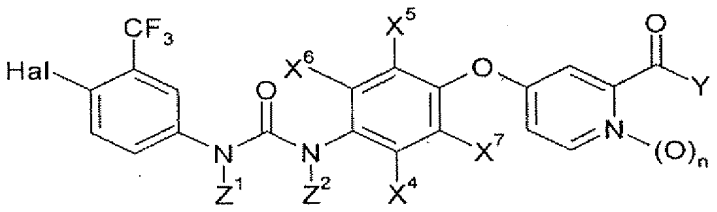
4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,

4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-N-hydroxymethyl-2-pyridine carboxamide 1-oxide,

4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide 1-oxide,

4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide 1-oxide, salts thereof and stereoisomers thereof.

28. (Previously Presented) A compound of formula (II), or a salt or stereoisomer thereof,



II

wherein,

Y	is OR^1 or NHR^2,
Hal	is chlorine or bromine,
R^1	is H or C_1-C_6 alkyl,
R^2	is H, OH, CH_3 or CH_2OH,
Z^1 and Z^2	are each H or OH, wherein only one of Z^1 or Z^2 is OH,
X^4 to X^7	are each, independently, H , OH or $O(CO)C_1$-C_4 alkyl, and
n	is 0 or 1,

with the proviso that at least one of conditions a-c is met,

a) Z^1 or Z^2 is OH,

b) Y is NHR^2 and R^2 is OH,

c) n is 1.

29. (Original) A compound of claim 28, wherein in formula (II), n is 1.

30. (Original) A compound of claim 29, wherein in formula (II), Z^1 and Z^2 are each H.

31. (Original) A compound of claim 30, wherein in formula (II), at least one of X^4 to X^7 is OH.

32. (Original) A compound of claim 30, wherein in formula (II), Y is NHR^2 and R^2 is H or CH_3.

33. (Original) A compound of claim 28, wherein in formula (II), n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H.

34. (Original) A compound of claim 28, wherein in formula (II), n is 0, Z^1 and Z^2 are each H, and at least one of X^4 to X^7 is OH.

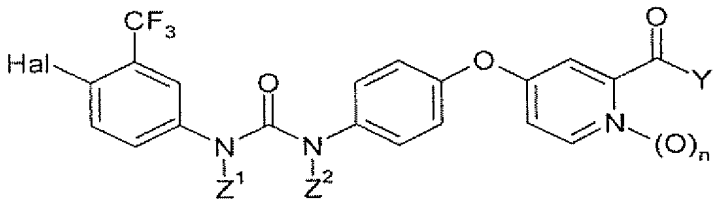
35. (Original) A compound of claim 33, wherein in formula (II), at least one of X^4 to X^7 is OH.

36. (Original) A compound of claim 33, wherein in formula (II), Y is NHR^2 and R^2 is H or CH_3.

37. **(Original)** A compound of claim 33, wherein in formula (II) Y is NHR^2 and R^2 is OH.

38 **(Original)** A compound of claim 37, wherein in formula (II), at least one of X^4 to X^7 is OH.

39. **(Previously Presented)** A compound of formula (III), or a salt or isolated stereoisomer thereof,



III

wherein,

Y	is OR^1 or NHR^2,
Hal	is chlorine or bromine,
R^1	is H or C_1-C_6 alkyl,
R^2	is H, OH, CH_3 or CH_2OH,
Z^1 and Z^2	are each H or OH, wherein only one of Z^1 or Z^2 can be OH, and
n	is 0 or 1,

with the proviso that at least one of conditions a-c is met,

a) Z^1 or Z^2 is OH,

b) Y is NHR^2 and R^2 is OH,

c) n is 1.

40. (Original) A compound of claim 39, wherein in formula (III), n is 1 and Z^1 and Z^2 are each H.

41. (Original) A compound of claim 40, wherein in formula (III), Y is NHR^2 and R^2 is H or CH_3,

42. (Original) A compound of claim 39, wherein in formula (III), n is 0 and Z^1 is H and Z^2 is OH or Z^1 is OH and Z^2 is H,

43. (Original) A compound of claim 42, wherein in formula (III), Y is NHR^2 and R^2 is H or CH_3.

44. (Original) A compound of claim 39, wherein in formula (III), Y is OH.

45. (Cancelled)

46. (Previously Presented) A method of preparing compounds of claim 1, comprising oxidizing:

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-chloro-3-trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino] phenoxy}-2-pyridine carboxamide to :

a) replace one or more of the phenyl hydrogens at the positions represented by X^1 to X^7 with a hydroxyl group,

b) hydroxylate the N-methyl amide into a hydroxymethyl amide or hydroxamic acid,

c) demethylate the N-methyl amide into an unsubstituted amide,

d) replace one or more of the urea nitrogens (=NH) with a hydroxyl group to form an N-hydroxyurea (=NOH),

e) hydrolyze the N-methyl amide into a carboxylic acid,

f) oxidize the pyridyl ring nitrogen to form the corresponding pyridine-1-oxide, or

g) provide a combination of two or more of a) - f);

with the proviso that at least one of b), d) and f) is performed.

47. (Original) A method as in claim 46 wherein oxidation of

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-chloro-3-trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl)

phenyl]amino}carbonyl)amino] phenoxy}-2-pyridine carboxamide replaces one or more hydogens at the positions represented by X^1 to X^7 with a hydroxyl group and at least one of the hydroxyl groups in the X^1 to X^7 positions is esterified.

48. (Original) A method as in claim 46 which prepares

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,

4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-pyridine carboxamide 1-oxide,

4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-pyridine carboxamide 1-oxide, or a pharmaceutically acceptable salt of one of these oxides, or an isolated stereoisomer of one of these oxides.

49. (Original) A pharmaceutical composition comprising an effective amount of at least one compound of claim 1 and a physiologically acceptable carrier.

50. (Original) A pharmaceutical composition comprising an effective amount of

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide, 4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide 1-oxide,

4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy}2-

pyridine carboxamide 1-oxide,

4-{4-[({[4-bromo-3-(trifluoromethyl)phenyl] amino}carbonyl)amino]phenoxy} 2-pyridine carboxamide 1-oxide or

a pharmaceutically acceptable salt of one of these oxides, an isolated stereoisomer of one of these oxides or a mixture thereof and a physiologically acceptable carrier.

51. (Original) A method of treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of cancer, in a mammal by administering an effective amount of a compound of claim 1 to said mammal.

52. (Original) A method as in claim 51 wherein the compound of claim 1 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

53. (Original) A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering an effective amount of a compound of claim 1 to said mammal.

54. (Original) A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering an effective amount of a compound of claim 27 to said mammal.

55. **(Withdrawn)** A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering to said mammal a) an effective amount of a compound of claim 1 and b) an additional anti-proliferative agent.

56. **(Withdrawn)** A method as in claim 55 wherein the compound of claim 1 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

57. **(Withdrawn)** A method as in claim 56 wherein the pharmaceutical composition comprises an effective amount of a compound of claim 1, a physiologically acceptable carrier and the additional anti-proliferative agent.

58. **(Withdrawn)** A method as in claim 56 wherein the additional anti-proliferative agent administered is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

59. **(Withdrawn)** A method as in claim 56 wherein the additional anti-proliferative agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine,

raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine,

aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, oxaliplatin, gemcitabone, gefinitib, taxotere, BCNU, CCNU, DTIC, ara A, ara C, herceptin, actinomycin D, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

60. (Withdrawn) A method of treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of raf-mediated cancer, in a mammal by administering an effective amount of a compound of claim 27 to said mammal.

61. (Withdrawn) A method of treating or preventing cancer by administering to a mammal

a) an effective amount of a compound of claim 1, and

b) a cytotoxic agent or cytostatic chemotherapeutic agent.

62. **(Withdrawn)** A method of claim 61 wherein the compound of claim 1 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

63. **(Withdrawn)** A method of claim 62 wherein the pharmaceutical composition comprises an effective amount of a compound of claim 1, a physiologically acceptable carrier and the cytotoxic agent or cytostatic chemotherapeutic agent.

64. **(Withdrawn)** A method of claim 62 wherein the cytotoxic agent or cytostatic chemotherapeutic agent administered is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of claim 1 and a physiologically acceptable carrier.

65. **(Withdrawn)** A method as in claim 61 wherein the cytotoxic or cytostatic chemotherapeutic agent is selected from the group consisting of DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, microtubule disruptors, hormone and growth factor receptor agonists or antagonists, other kinase inhibitors and anti-metabolites.

66. **(Withdrawn)** A kit comprising a separate dose of the cytotoxic or cytostatic agent and, a separate dose of a compound of claim 1.

67. **(Withdrawn)** A method of treating or preventing a hyper-proliferative disorder in a mammal comprising administering to said mammal a) an effective amount of a compound of claim 27 and b) an additional anti-proliferative agent.

68. **(Withdrawn)** A method wherein the compound of claim 27 administered is within a pharmaceutical composition comprising an effective amount of a compound of claim 27 and a physiologically acceptable carrier.

69. **(Withdrawn)** A method wherein the pharmaceutical composition comprises an effective amount of a compound of claim 27, a physiologically acceptable carrier and the additional anti-proliferative agent.

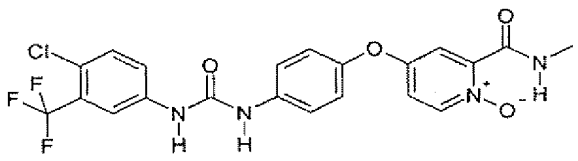
70. **(Withdrawn)** A method wherein the additional anti-proliferative agent administered is within a pharmaceutical composition separate from the pharmaceutical composition comprising an effective amount of a compound of claim 27 and a physiologically acceptable carrier.

71. **(Withdrawn)** A method as in claim 68 wherein the additional anti-proliferative agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine,

raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine,

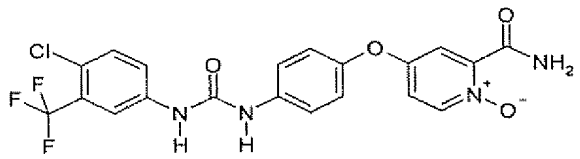
aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, oxaliplatin, gemcitabone, gefinitib, taxotere, BCNU, CCNU, DTIC, ara A, ara C, herceptin, actinomycin D, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

72. **(Original)** A method of preparing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)-1-oxo-(4-pyridyloxy)]phenyl} urea



comprising chemically oxidizing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-(N-methylcarbamoyl)(4-pyridyloxy)]phenyl} urea in solution.

73. **(Original)** method of preparing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-1-oxo-(4-pyridyloxy)]phenyl} urea



comprising chemically oxidizing N-[4-chloro-3-(trifluoromethyl)phenyl]-N'-{4-[2-carbamoyl-(4-pyridyloxy)]phenyl} urea in solution.

74. (Previously Presented) A derivative of one of the following compounds:

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide, or

4-{4-[({[4-chloro-3-trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino] phenoxy}-2-pyridine carboxamide

obtained by oxidizing the compound.

75. (Previously Presented) A derivative of one of the following compounds:

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-chloro-3-trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino] phenoxy}-2-pyridine carboxamide; wherein said derivative is obtained by

a) replacing one or more of the phenyl hydrogens at the positions represented by X^1 to X^7 with a hydroxyl group,

b) hydroxylating the N-methyl amide where present, into a hydroxymethyl amide or hydroxamic acid,

c) replacing one or more of the urea nitrogens (=NH) with a hydroxyl group to form an N-hydroxyurea (=NOH),

d) hydrolyzing the N-methyl amide where present, into a carboxylic acid,

e) oxidizing the pyridyl ring nitrogen to form the corresponding pyridine-1-oxide, or

f) providing a combination of two or more of a) - e);

with the proviso that at least one of b), d) and f) is performed.

76. **(Previously Presented)** A derivative of one of the following compounds:

4-{4-[({[4-chloro-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-N-methyl-2-pyridine carboxamide,

4-{4-[({[4-chloro-3-trifluoromethyl) phenyl]amino}carbonyl)amino]phenoxy}-2-pyridine carboxamide, or

4-{4-[({[4-bromo-3-(trifluoromethyl) phenyl]amino}carbonyl)amino] phenoxy}-2-pyridine carboxamide

obtained by

a) replacing one or more of the phenyl hydrogens with a hydroxyl group on one of the compounds above and

b) esterifying at least one of these hydroxyl groups.

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) A composition comprising a N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea or a pharmaceutically acceptable salt thereof and a cytotoxic or cytostatic agent selected from the group consisting of: irinotecan, vinorelbine, gemcitabine, gefitinib, [[,]] paclitaxel, and doxorubicin.

2. (Original) The composition according to claim 1, in combination with one or more pharmaceutically acceptable carrier molecules.

3. (Previously Presented) The composition of claim 1, wherein said pharmaceutically acceptable salt of N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea is a tosylate salt.

4. (Previously Presented) A composition according to claim 1, in the form of an oral, intramuscular, intravenous, subcutaneous, or parenteral dosage which can range from about 0.1 to about 300 mg/kg of total body weight of N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea and from about 0.1 to about 300 mg/kg of total body weight of a cytotoxic or a cytostatic agent.

5. (Currently Amended) A method for treating a cancer comprising administering a therapeutically effective amount of a composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea or a

pharmaceutically acceptable salt thereof and a cytotoxic or cytostatic agent selected from the group consisting of: irinotecan, vinorelbine, gemcitabine, gefitinib, [[;]] paclitaxel, and doxorubicin.

6. (Previously Presented) The method of claim 5, wherein said pharmaceutically acceptable salt of N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea is a tosylate salt.

7. (Original) The method of claim 5, wherein said cancer is mediated by raf kinase.

8. (Original) The method of claim 5, wherein said cancer is colon, gastric, lung, pancreatic, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, glioma, mammary, or head and neck cancer.

9. (Previously Presented) The method of claim 5, wherein said composition is administered to a patient at an oral, intramuscular, intravenous, subcutaneous, or parenteral dosage which can range from about 0.1 to about 300 mg/kg of total body weight of N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea and from about 0.1 to about 300 mg/kg of total body weight of a cytotoxic or a cytostatic agent.

10. (Previously Presented) A composition comprising a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea and a cytotoxic or cytostatic agent selected from the group consisting of: irinotecan, vinorelbine, gemcitabine, gefitinib, paclitaxel, and doxorubicin.

11. (Currently Amended) A method for treating a cancer comprising administering a therapeutically effective amount of a composition comprising a tosylate salt of ~~N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)~~ N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea and a cytotoxic or cytostatic agent selected from the group consisting of: irinotecan, vinorelbine, gemcitabine, gefitinib, paclitaxel, and doxorubicin.

12. (Previously Presented) A method for inhibiting the proliferation of cancer cells in a patient comprising contacting said cancer cells with a pharmaceutical preparation comprising the composition of claim 1.

13. (New) A method according to claim 5, wherein a therapeutically effective amount of a composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea or a pharmaceutically acceptable salt thereof and a cytotoxic or cytostatic agent selected from the group consisting of: irinotecan, vinorelbine, gemcitabine, gefitinib, and paclitaxel are administered.

14. (New) A method according to claim 5, wherein pancreatic tumor is treated by the administration of a therapeutically effective amount of a composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea or a pharmaceutically acceptable salt thereof and gemcitabine.

15. (New) A method according to claim 5, wherein non-small cell lung tumor is treated by the administration of a therapeutically effective amount of a composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-

pyridoxy)phenyl)urea or a pharmaceutically acceptable salt thereof and vinorelbine, or gefitinib.

16. (New) A method according to claim 5, wherein mammary tumor is treated by the administration of a therapeutically effective amount of a composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea or a pharmaceutically acceptable salt thereof and doxorubicin.

17. (New) A method according to claim 5, wherein colon tumor is treated by the administration of a therapeutically effective amount of a composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea or a pharmaceutically acceptable salt thereof and irinotecan.

18. (New) A composition according to claim 10, which comprises a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-methylcarbamoyl)-4-pyridoxy)phenyl)urea and a cytotoxic or cytostatic agent selected from the group consisting of: irinotecan, vinorelbine, gemcitabine, gefitinib, and paclitaxel.

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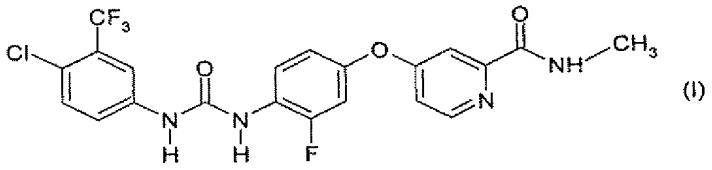
Claims

1. A compound of Formula (I) or a salt, or a prodrug or a metabolite or an isolated stereoisomer thereof



(I)

2. A pharmaceutically acceptable salt of a compound of Formula I of claim 1 which is

a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

3. A compound which is 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide, or a salt thereof.

4. A pharmaceutically acceptable salt of a compound of claim 3 which is a basic salt of an organic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic

acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid.

5. A compound which is which is a hydrochloride, benzenesulfonate, or methanesulfonate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-2-fluoro-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea.

6. A pharmaceutical composition comprising a compound of claim 1 and a physiologically acceptable carrier.

7. A pharmaceutical composition comprising a compound of claim 3 and a physiologically acceptable carrier.

8. A pharmaceutical composition for the treatment of a disease in a human or other mammal regulated by a protein kinase, associated with an aberration in the protein kinase signal transduction pathway comprising a compound of claim 1 and a physiologically acceptable carrier.

9. A pharmaceutical composition for the treatment of a hyper-proliferative disorder comprising a compound of claim 1 and a physiologically acceptable carrier.

10. A pharmaceutical composition for the treatment of a cancerous cell growth comprising a compound of claim 1 and a physiologically acceptable carrier.

11. A pharmaceutical composition which comprises a pharmaceutically acceptable salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-2-fluoro-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea and a physiologically acceptable carrier.

12. A method for regulating tyrosine kinase signal transduction comprising administering to a human or other mammal a compound of claim1.

13. A method for treating or preventing a disease in a human or other mammal which is regulated by tyrosine kinase and associated with an aberration in the tyrosine kinase signal transduction pathway, said method comprising administering to a human or other mammal a compound of claim 1.

14. A method for treating or preventing a disease in a human and/or other mammal which is a VEGFR-2 mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

15. A method for treating or preventing a disease in a human and/or other mammal which is a PDGFR mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

16. A method for treating or preventing a disease in a human or other mammal which is a raf-mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

17. A method for treating or preventing a disease in a human or other mammal which is a p38-mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

18. A method for treating or preventing a disease in a human or other mammal which is a VEGF-mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

19. A method for treating or preventing a disease in a human or other mammal which is a hyper-proliferative, inflammatory and/or angiogenesis disorder which comprises administering to a human or other mammal a compound of claim 1.

20. A method for treating or preventing a disease in a human or other mammal which is a hyper-proliferative disorder which comprises administering to a human or other mammal a compound of claim 1.

21. A method as in claim 20, wherein the hyper-proliferative disorder is cancer.

22. A method as in claim 21, wherein said method comprises administering to a human or other mammal a compound of claim 1 in combination with one or several additional anti-cancer agents.

23. A method for treating or preventing a disease in a human or other mammal characterized by abnormal angiogenesis or hyperpermiability processes comprising administering to a human or other mammal a compound of claim 1.

24. A method as in claim 23, for treating or preventing a disease in a human or other mammal characterized by abnormal angiogenesis or hyperpermeability processes, comprising administering to a human or other mammal, a compound of claim 1 simultaneously with another anti-angiogenesis agent, either in the same formulation or in separate formulations.

25. A method for treating or preventing one or more of the following conditions in humans and/or other mammals:

tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis, rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, cornal ulceration, proteinuria and coronary thrombosis from atherosclerotic plaque, aneurismal aortic, birth control, dystrophobic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, tempero mandibular joint disease or demyelating disease of the nervous system,

said method comprising administering to a human or other mammal, a compound of claim 1.

26. A method for treating or preventing one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis;

in combination with another condition selected from the group consisting of:

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Krohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (Plasmodium falciparum malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) and complications due to total hip replacement,

said method comprising administering to a human or other mammal a compound of claim 1.

27. A method for treating or preventing one or more of the following conditions in humans and/or other mammals: tumor growth, retinopathy, diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, age related macular degeneration; rheumatoid arthritis, psoriasis, bullous disorder associated with subepidermal blister formation, bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis,

in combination with an infectious disease selected from the group consisting of :

tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV);

said method comprising administering to a human or other mammal a compound of claim 1.

28. A method as in claim 22 wherein the additional anti-cancer agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2',2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyl adenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine, oxaliplatin, gemcitabine, capecitabine, epothilone and its natural or synthetic derivatives, tositumomab, trabedectin, and temozolomide. trastuzumab, cetuximab, bevacizumab, pertuzumab, ZD-1839 (Iressa), OSI-774 (Tarceva), CI-1033, GW-2016, CP-724,714, HKI-272, EKB-569, STI-571 (Gleevec), PTK-787, SU-11248, ZD-6474, AG-13736, KRN-951, CP-547,632, CP-673,451, CHIR-258, MLN-518, AZD-2171, PD-325901, ARRY-

142886, suberoylanilide hydroxamic acid (SAHA), LAQ-824, LBH-589, MS-275, FR-901228, bortezomib, and CCI-779.

29. A method as in claim 22 wherein the additional anti-cancer agent is a cytotoxic agent selected from the group consisting of DNA topoisomerase I and II inhibitors, DNA intercalators, alkylating agents, anti-metabolites, cell-cycle blockers, microtubule disruptors, and Eg5 inhibitors.

30. A method as in claim 22 wherein the additional anti-cancer agent is selected from the group consisting of inhibitors of growth factor receptor signaling, histone deacetylase inhibitors, inhibitors of the PKB pathway, inhibitors of the Raf/MEK/ERK pathway, inhibitors of the mTOR pathway, and proteasome inhibitors.

31. A method for treating or preventing one or more of the following conditions in humans and/or other mammals:

rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Krohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction, asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (Plasmodium falciparum malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement,

said method comprising administering to a human or other mammal, a compound of claim 1.

32. A method for treating or preventing one or more of the following conditions in humans and/or other mammals:

tuberculosis, Helicobacter pylori infection during peptic ulcer disease, Chaga's disease resulting from Trypanosoma cruzi infection, effects of Shiga-like toxin resulting from E. coli infection, effects of enterotoxin A resulting from Staphylococcus infection, meningococcal infection, and infections from Borrelia burgdorferi, Treponema pallidum, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV) ,

said method comprising administering to a human or other mammal, a compound of claim 1.

33. A method for treating or preventing osteoporosis, inflammation, and angiogenesis disorders, with the exclusion of cancer, in a human and/or other mammal by administering an effective amount of a compound of claim 1 to said mammal.

34. A method for treating or preventing cancer in a human or other mammal which comprises administering to a human or other mammal a single active principle combining inhibition of tumor cell proliferation mediated by the raf / MEK / ERK pathway, and inhibition of angiogenesis mediated by PDGF and VEGF.

35. A method of claim 34 where said inhibition of tumor cell proliferation is caused by inhibition of raf kinase, and said inhibition of angiogenesis is caused by dual inhibition of PDGFR-beta and VEGFR-2 kinases.

36. A method for treating or preventing cancer in a human or other mammal which comprises administering to a human or other mammal a single active principle combining inhibition of tumor cell proliferation mediated by the raf pathway, and inhibition of angiogenesis mediated by PDGF or VEGF.

37. A method of treating and/or preventing a disease and/or condition in a subject in need thereof, comprising administering an effective amount of a compound of claim 1 or 2.

38. A method of claim 37, wherein said method comprises causing tumor regression in a subject or cells therefrom.

39. A method of claim 37, wherein said method comprises inhibiting lymphangiogenesis.

40. A method of claim 37, wherein said method comprises inhibiting angiogenesis.

41. A method of claim 37, wherein said method comprises inhibiting lymphangiogenesis and angiogenesis.

42. A method of claim 37, wherein said method comprises stimulating the proliferation of hematopoietic progenitor cells.

43. A method of claim 37, wherein said method comprises treating a disorder in a mammalian subject mediated by raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38 and/or flt-3.

44. A method of claim 37, wherein said method comprises determining whether a condition can be modulated by said compound, comprising measuring the expression or activity of raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38 and/or flt-3, in a sample comprising cells or a cell extract, wherein said ample is obtained from a subject or cell having said condition, whereby said condition can be modulated by said compound when said expression or activity is different in said condition as compared to a normal control.

45. A method of claim 44, further comprising comparing the expression in said sample to said normal control.

46. A method of claim 37, wherein said method comprises assessing the efficacy of said compound disorder, comprising administering said compound, measuring the expression or activity of raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38, and/or flt-3, and determining the effect of said compound on said expression or activity.

47. A method of claim 37, wherein said method comprises determining the presence of raf, VEGFR-2, VEGFR-3, PDGFR-beta, p38 and/or flt-3 in a sample of a biological material, contacting said sample with said compound, and determining whether said compound binds to said material.

48. A method of claim 37, wherein said method comprises treating a tumor in a subject in need thereof, comprising administering an effective amount of said compound wherein said amount is effective to inhibit tumor cell proliferation and neovascularization.

49. A compound which is a naturally occurring metabolite of the compound of claim 3.

50. A compound of claim 49 where the metabolism site is either one of the two urea nitrogen atoms, or the pyridine nitrogen atom, or the methylamide functionality, or any combination of the above.

51. A compound of claim 49 where either urea nitrogen atom carries a hydroxyl group, and/or the pyridine nitrogen atom is oxidized, and/or the amide functionality is de-methylated.

52. A compound of claim 49 which is selected from:
4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid amide,
4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-1-hydroxy-pyridine-2-carboxylic acid methylamide, or
4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-1-hydroxy-pyridine-2-carboxylic acid amide.

53. A method as in claim 19, where the inflammatory disorder is selected from rheumatoid arthritis, COPD, Crohn's disease and proriasis.

54. A method for treating or preventing a disease in a human or other mammal which is a flt-3 mediated disorder, said method comprising administering to a human or other mammal a compound of claim 1.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 6 of 8

Complete if Known	
Application Number	10/086,417
Filing Date	March 4, 2002
First Named Inventor	Bernd Riedl et al.
Group Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	BAYER 16P4

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	AA	A "Notice of References Cited" from the USPTO for U.S. application 08/995,749.	
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	AK	A "Notice of References Cited" from the USPTO for U.S. application 09/773,672.	
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Sheet 7 of 8

Complete if Known	
Application Number	10/086,417
Filing Date	March 4, 2002
First Named Inventor	Bernd Riedl et al.
Group Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	BAYER 16P4

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	AN	A "Notice of References Cited" from the USPTO for U.S. application 09/776,936.	
	AO	A "Notice of References Cited" from the USPTO for U.S. application 09/777,920.	
	AP	A "Notice of References Cited" from the USPTO for U.S. application 09/948,915.	
	AQ	A "Notice of References Cited" from the USPTO for U.S. application 10/042,226.	
	AR	A "Notice of References Cited" from the EPO fro European application EP 98/963809.	
	AS	Supplemental search report from the EPO for European application EP 98/963810.	
	AT	Supplemental search report from the EPO for European application EP 98/965981.	
	AU	Supplemental search report from the EPO for European application EP 00/903239.	
	BA	International search report for International Application No. PCT/US98/10375.	
	BB	International search report for International Application No. PCT/US98/10376.	

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Sheet 8 of 8

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	BC	International search report for International Application No. PCT/US98/26078.	
	BD	International search report for International Application No. PCT/US98/26079.	
	BE	International search report for International Application No. PCT/US98/26080.	
	BF	International search report for International Application No. PCT/US98/26081.	
	BG	International search report for International Application No. PCT/US98/26082.	
	BH	International search report for International Application No. PCT/US98/24265.	
	BI	International search report for International Application No. PCT/US00/00648.	
	BJ	International search report for International Application No. PCT/US00/00768.	
	BK	International search report for International Application No. PCT/US02/12064.	
	BL	International search report for International Application No. PCT/US02/12066.	
	BM	International search report for International Application No. PCT/US/26081.	

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